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TITLE:

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Safety and Insulin-Sparing Efficacy of the Addition of Sitagliptin in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Insulin Alone or in Combination With Metformin

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: III

US IND NUMBER: 65,495

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

TABLE OF CONTENTS

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

Section Numbers	Section Titles	Description of Changes
3.5.3.3	Derivation of Efficacy Endpoints	An efficacy endpoint, A1C-to-insulin ratio, has been added, to be used for sensitivity analyses.
3.5.4.1	Efficacy Analysis Populations	Analysis populations have been defined for the A1C-to-insulin ratio.
3.5.5.1	Statistical Methods for Efficacy Analyses	• A normality test has been added for the primary endpoint, along with methodology to be used if the data are found to be non-normal. • Methodology for the A1C-to-insulin ratio has been added. • A1C-to-insulin ratio has been added to Table 3-2.
6.6.1	[redacted]	[redacted]
6.6.3	[redacted]	[redacted]

OTHER CHANGES INCLUDED IN THE AMENDMENT:

Section Numbers	Section Titles	Description of Changes
		Note: The first two items are new, the rest of the listed items were previously communicated as part of 3 separate Protocol Clarification Letters (PCLs).

3.2.3.2	Assessment and Management of Hypoglycemia	Clarified that each event of symptomatic hypoglycemia must be reported as an adverse event on the adverse event electronic case report form (eCRF), as this is not up to the Investigator's discretion. It is up to the Investigator's discretion as to whether an episode of asymptomatic hypoglycemia is considered an adverse event; if so, it too should be reported on the adverse event eCRF.
3.4.6.2.2	Guidance	Clarified that all episodes considered as likely to represent symptomatic hypoglycemia by the investigator must be captured as an adverse event of "symptomatic hypoglycemia."
1.7	Study Flow Chart	**Footnote #2**: Removed statement regarding the use of Visit 1 A1C criterion to assess eligibility at a combined V2/V3. This statement was not applicable since A1C entry criterion is only assessed at Visit 1. **Footnote #4**: Clarified that plasma and serum samples for Future Biomedical Research (FBR) must be collected pre-dose at Visit 4. In addition, plasma and serum can only be collected at specified visits, Visit 4 and Visit 9 (or Discontinuation Visit). **Footnote #12**: Clarified that in order to meet Visit 1 Inclusion Criteria #2, fasting C-peptide must be collected if patients were diagnosed before 40 years old or (as opposed to "and") if therapy was initiated within 3 years after diagnosis.

1.7	Study Flow Chart (cont)	**Footnote #13**: Clarified that if a patient is not fasting at Visit 1, fasting C-peptide must be obtained prior to Visit 2, and can't be obtained at Visit 2. **Footnote #14**: Clarified that if a patient is not fasting at Visit 1, a fasting lipid profile must be obtained prior to Visit 2, and can't be obtained at Visit 2. **Footnote #18**: Clarified to be consistent with Inclusion Criteria #6. Follicle-stimulating hormone (FSH) should be obtained in women ≤ 45 years of age who have spontaneous amenorrhea for ≥6 months, and in women >45 years of age who have spontaneous amenorrhea for ≥6 months but <12 months.
2.3	Patient Exclusion Criteria	**Exclusion Criteria #27**: Clarified that a clinically significant ECG abnormality during the run-in period (removed "screening visit," since ECG is not performed at that visit) would meet exclusion criteria.
2.4.1.2	Visit 1/Screening Visit	Clarified that if a patient is not fasting at Visit 1, a fasting lipid profile and fasting C-peptide should be obtained prior to Visit 2, not at Visit 2. However, if not fasting at Visit 1, a fasting plasma glucose (FPG) may be obtained at or prior to Visit 2.
2.4.1.3	Visit 2	Clarified that an unscheduled visit to monitor a patient's glycemic control is only needed if the fasting fingerstick glucose (FFSG) value is persistently >260 mg/dL (14.4 mmol/L) or persistently ≤ 70 mg/dL (3.9 mmol/L). Otherwise, the evaluation can occur via telephone call.

3.2.3.5	Electrocardiogram (ECG) Procedures	Clarified that a local ECG will be performed at Visit 3, not at Visit 2, this is now consistent with other relevant sections of the protocol.
6.1	[redacted]	[redacted]
6.2	[redacted]	[redacted]
6.5	[redacted]	[redacted]
7.0	[redacted]	[redacted]

1. SUMMARY

1.1 TITLE

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Safety and Insulin-Sparing Efficacy of the Addition of Sitagliptin in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Insulin Alone or in Combination With Metformin

1.2 INDICATION

Use of sitagliptin in patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control on insulin alone or in combination with metformin.

1.3 SUMMARY OF RATIONALE

The purpose of the present study is to examine the insulin-sparing effect of sitagliptin 100 mg once-daily compared with placebo over 24 weeks in patients with T2DM who have inadequate glycemic control on insulin alone or in combination with metformin.

1.4 SUMMARY OF STUDY DESIGN

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trial. The duration of the study will be up to 29 weeks (with 9 clinic visits) for each patient. This will include a 1-week screening period (**Visit 1/Screening Visit to Visit 2**); an insulin switch (for patients not on insulin glargine once-daily in the evening) and sulfonylurea "wash-off" (for patients on sulfonylurea) period of 2 weeks (**Visit 2 to Visit 3/Week -2**)**;** a 2-week single-blind placebo run-in period (**Visit 3/Week -2 to Visit 4/Day 1**], and a 24-week double-blind treatment period **(Visit 4/Day 1 to Visit 9/Week 24)**. Patients with T2DM on a stable dose of insulin glargine in the evening alone or in combination with metformin (≥1500 mg/day) at **Visit 1/Screening Visit** and who meet all other enrollment criteria will *directly* enter into the 2-week single-blind placebo run-in period at a combined **Visit 2/3** (since these patients will go from **Visit 1/Screening Visit** to **Visit 3/Week -2**, the **Visit 3/Week -2** visit will be referred to as a "combined" (**Visit 2/3/Week -2)**. For details on the run-in duration and visit schedule, see Section 2.4.

At **Visit 1/Screening Visit** patients who meet the following criteria **and** who satisfy all other entry criteria will be eligible to continue to **Visit 2**:

- On a stable dose (**≥15 U/day and ≤150 U/day**) of insulin for **at least 10 weeks** [basal insulin only (NPH, glargine, detemir) once-daily or twice-daily or pre-mixed insulin (at least 70% basal) once-daily or twice-daily excluding patients with only prandial insulin or basal/bolus regimens]

- With or without metformin (immediate-release or extended-release formulation) at ≥1500 mg/day for at least 10 weeks

- With or without a sulfonylurea for at least 10 weeks

AND

- Have inadequate glycemic control (i.e., hemoglobin **A_{1c} [A1C] ≥7.5% and ≤11.0%** for patients not on sulfonylurea and **A1C ≥7.0% and ≤10.0%** for patients on sulfonylurea)

At **Visit 2/Week -4**, eligible patients will enter the insulin switch (for those not on insulin glargine once-daily in the evening) and sulfonylurea "wash-off" (for patients on sulfonylurea) period for 2 weeks. During this time, patients will discontinue all sulfonylurea therapy (if applicable) and switch to locally-sourced, open-label insulin glargine. If on metformin, they will switch to locally-sourced open-label metformin at their current dose. At **Visit 3/Week -2**, eligible patients will enter the 2-week single-blind placebo run-in period. At **Visit 4/Day 1**, patients who meet the study enrollment criteria will enter the double-blind treatment period, and will be randomized in a 1:1 ratio to receive either sitagliptin 100 mg or matching placebo once-daily. Patients will continue on their stable doses of metformin. From **Visit 5/Week 2,** through **Visit 9/Week 24** the patients will be instructed to titrate their insulin glargine dose based on their fasting fingerstick glucose (FFSG) values or fasting plasma glucose (FPG) values to improve glycemic control (treat-to-target of fasting glucose 72-100 mg/dL [4.0-5.6 mmol/L]). See Section 2.4.1.7.

A telephone contact will be performed 14 days after the last dose of study medication (due to study completion or premature discontinuation from the study) to assess for any serious adverse events (SAEs).

1.5 SAMPLE

Approximately 600 patients will be randomized. Patients who are 18 to 80 years of age at screening with T2DM and inadequate glycemic control (A1C at screening ≥7.5% and ≤11.0% for patients not on sulfonylurea and ≥7.0% and ≤10.0% for patients on sulfonylurea) on a stable dose of insulin glargine once-daily in the evening with or without metformin (≥1500 mg/day) for ≥10 weeks and after wash-off of sulfonylurea therapy (if on a sulfonylurea at screening), with a FFSG of ≥130 mg/dL (7.2 mmol/L) and ≤270 mg/dL (15.0 mmol/L), will be eligible for randomization into the study if they meet all other enrollment criteria.

For details surrounding patient definition, see Sections 2.2 "Patient Inclusion Criteria" and 2.3 "Patient Exclusion Criteria".

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

Sitagliptin (100 mg) and its matching placebo will be supplied as oral tablets in a blinded manner. During the 2-week single-blind placebo run-in period (**Visits 3/Week -2 to Visit 4/Day 1**), patients will take one tablet of placebo matching sitagliptin 100 mg once-daily. During the 24-week double-blind treatment period (**Visits 4/Day 1 to Visit 9/Week 24**), patients will take one tablet of sitagliptin 100 mg or matching placebo once-daily.

Open-label insulin glargine (LANTUS®) and metformin (immediate-release or extended-release formulation) will be obtained locally by the applicable subsidiary, investigational sites, or by prescription. The dose of metformin will remain stable throughout the study period. Beginning at **Visit 5/Week 2**, the dose of insulin will be titrated in a treat-to-target algorithm outlined in the protocol (Section 2.4.1.7).

1.7 STUDY FLOW CHART

	Pre-randomization			Random-ization	Randomized Treatment Phase										Discon-tinuation Visit	Poststudy Telephone Contact + 14 Days[3]
	Visit 1[1]	Visit 2[2]	Visit 3	Visit 4	Visit 5	PTC	Visit 6	PTC	PTC	Visit 7	PTC	Visit 8	PTC	Visit 9		
			Week -2	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 15	Week 18	Week 21	Week 24		
STUDY PERIODS																
Wash off sulfonylurea therapy and/or convert to insulin glargine (if applicable)		X----------X														
Single-blind placebo run-in			X----------X													
Double-blind treatment				X----------X												
Insulin titration (treat-to-target)					X----------X											
STUDY PROCEDURES																
Post-study telephone contact																X
Obtain informed consent	X															
Obtain informed consent for Future Biomedical Research[4]	X															
Dispense patient identification card		X														
Evaluate inclusion/exclusion criteria	X		X	X												
Monitor adverse events (AEs)		X	X	X	X		X			X		X		X	X	
Collect medical history[5]	X															
Review prior/concomitant medication	X	X	X	X	X		X			X		X		X	X	
Vital signs [Pulse Rate and Blood Pressure[6] (measured in duplicate)]	X		X	X	X		X			X		X		X	X	

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	Pre-randomization			Random-ization	Randomized Treatment Phase										Discon-tinuation Visit	Poststudy Telephone Contact + 14 Days[3]
	Visit 1[1]	Visit 2[2]	Visit 3	Visit 4	Visit 5	PTC	Visit 6	PTC	PTC	Visit 7	PTC	Visit 8	PTC	Visit 9		
			Week -2	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 15	Week 18	Week 21	Week 24		
STUDY PROCEDURES (CONT.)																
Weight[6] (measured in duplicate)	X			X	X		X			X		X		X	X	
Height[6] (measured in duplicate)	X															
Perform physical exam[7]				X										X	X	
Perform 12-lead electrocardiogram (ECG) read locally [8]			X													
Counsel to discontinue sulfonylurea therapy (if applicable)		X														
Switch to insulin glargine once-daily in the evening (if applicable)		X														
INSTRUCTION/COUNSELING																
Diet and exercise counseling/monitoring[9]		X	X	X	X		X			X		X		X	X	
Dispense Hypoglycemia Assessment Log (HAL) and instruct on hypoglycemia symptoms and management		X														
Dispense blood glucose meter and provide instruction on Self-Monitoring Blood Glucose (SMBG)		X														
OTHER MONITORING/ TESTS																
Site fingerstick Hemoglobin A_{1C} (A1C)	X[10]															
Site fasting fingerstick glucose (FFSG)				X												

03-May-2013

	Pre-randomization			Random-ization	Randomized Treatment Phase										Discon-tinuation Visit	Poststudy Telephone Contact + 14 Days[3]
	Visit 1[1]	Visit 2[2]	Visit 3	Visit 4	Visit 5	PTC	Visit 6	PTC	PTC	Visit 7	PTC	Visit 8	PTC	Visit 9		
			Week -2	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 15	Week 18	Week 21	Week 24		
OTHER MONITORING/ TESTS (CONT.)																
Review of SMBG measurements and HAL			X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess patient for treat-to-target therapy based on FFSG					X	X	X	X	X	X	X	X	X			
CENTRAL LABORATORY TEST																
Fasting plasma glucose (FPG)	X[11]		X	X	X		X			X		X		X	X	
Hemoglobin A_{1C} (A1C)	X			X			X			X		X		X	X	
Complete blood count (CBC)/differential	X			X						X				X	X	
Chemistry panel	X			X						X				X	X	
Fasting C-Peptide [12]	X[13]															
Lipid panel	X[14]			X[15]										X	X	
Thyroid stimulating hormone (TSH) [16]	X															
Dipstick urinalysis [17]	X			X										X	X	
Follicle-stimulating hormone (FSH)[18]	X															
Urine pregnancy test (for women of childbearing potential) [19]	X		X	X	X		X			X		X		X	X	

	Pre-randomization			Random-ization	Randomized Treatment Phase										Discon-tinuation Visit	Poststudy Telephone Contact + 14 Days[3]
	Visit 1[1]	Visit 2[2]	Visit 3	Visit 4	Visit 5	PTC	Visit 6	PTC	PTC	Visit 7	PTC	Visit 8	PTC	Visit 9		
			Week -2	Day 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 15	Week 18	Week 21	Week 24		
CENTRAL LABORATORY TEST (CONT.)																
Blood sample (plasma and serum) for Future Use[4]				X										X	X	
Blood for Future Biomedical Research[4]				X												
STUDY MEDICATION																
Dispense single-blind placebo run-in medication			X													
Monitor for single-blind placebo run-in compliance				X												
Dispense open-label insulin and open-label metformin (only to patients who are on metformin at screening)		X		X			X			X		X				
Dispense double-blind study medication				X			X			X		X				
Monitor compliance with double-blind study medication.					X		X			X		X		X	X	
Patient telephone contact (PTC)[20]						X		X	X		X		X			

1.	A patient consent form must be signed prior to any study specific procedures being performed and may be signed prior to **Visit 1/Screening Visit**.
2.	For patients not on a sulfonylurea (off for ≥10 weeks) and on insulin glargine once-daily in the evening +/- metformin, if **Visit 1/Screening Visit** A1C is ≥7.5% and ≤11.0%, a combined **Visit 2/3** may be performed. Patients requiring adjustment of lipid-lowering medication should NOT have visits combined. For combined visits, all procedures from each individual visit must be performed at the one combined visit.
3.	Patient will be contacted 14 days after the last dose of study medication (either after the completion of the 24-week treatment period or after early discontinuation from the study) to assess and collect SAEs
4.	The Future Biomedical Research (FBR) informed consent must be obtained before FBR samples for DNA analysis, plasma, and serum are collected. The FBR sample for DNA analysis should be obtained pre-dose, at Visit 4, as the last sample drawn, and on patients who qualify for randomization only. The sample may be obtained at a later date during the study after the FBR informed consent is obtained. The plasma and serum sample for FBR should be collected at Visit 4 (pre-dose) and at Visit 9 (or Discontinuation Visit for patients who discontinue prior to Visit 9).
5.	The use of tobacco should be collected as part of medical history.
6.	Refer to Appendix 6.1 for measuring techniques.
7.	Patients must have their physical exam performed prior to being randomized.
8.	ECGs will be read locally prior to patient being randomized and will not be sent to a central ECG reading laboratory.
9.	Patients will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at **Visit 2** only; follow-up at other visits may be done by other appropriate site personnel evaluating the patient.
10.	Site fingerstick A1C testing may be used, at the discretion of the investigator, for screening purposes only. However, a central laboratory A1C value must be used to assess inclusion criterion.
11.	If the patient is not fasting at **Visit 1/Screening Visit**, FPG blood sample should be obtained at or prior to **Visit 2** rather than at **Visit 1/Screening Visit**.
12.	At **Visit 1/Screening Visit**, fasting C-peptide should only be collected for patients who were diagnosed with diabetes before the age of 40 years or if insulin therapy was initiated within 3 years after the diagnosis of diabetes.
13.	If the patient is not fasting at **Visit 1/Screening Visit**, a fasting C-peptide should be obtained prior to **Visit 2** rather than at **Visit 1/Screening Visit**.
14.	If the patient is not fasting at **Visit 1/Screening Visit**, a fasting lipid profile should be obtained prior to **Visit 2** rather than at **Visit 1/Screening Visit**.
15.	Collection of a lipid panel is required at **Visit 4/ Day 1** only for those patients in whom, lipid medications were adjusted or otherwise required to reassess patient lipid profile. Patients on lipid-lowering medication must be on a stable regimen for the 4 weeks prior to **Visit 4/Day 1**.
16.	A patient excluded due to TSH criterion while on thyroid replacement therapy may be re-screened after being on a stable, adjusted thyroid replacement regimen for at least 6 weeks.
17.	If dipstick (midstream urine specimen) is positive for blood, WBC (e.g., leukocyte esterase, nitrates), or protein, then a urine sample for a complete urinalysis (dipstick and microscopy) should be sent to the central laboratory.
18.	FSH should be obtained in women ≤ 45 years of age who have spontaneous amenorrhea for ≥6 months, and in women >45 years of age who have spontaneous amenorrhea for ≥6 months but < 12 months.
19.	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)]. Patients with a positive urine pregnancy test during double-blind treatment period will interrupt study medication and undergo a serum pregnancy test.
20	At Weeks 4, 8, 10, 15, and 21, site personnel will contact patients by telephone to review insulin titration, monitor fingerstick glucose values (SMBG measurements), monitor the occurrence of episodes of hypoglycemia and instruct patients on insulin dose. They will also reinforce diet/exercise and review study therapy dosing instructions.

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary

In patients with T2DM with inadequate glycemic control on insulin with or without metformin, who titrate insulin glargine (Treat-to-Target):

(1) Objective: After 24 weeks, to assess the effect of sitagliptin compared with placebo on the change in insulin dose in IU per day.

Hypothesis: After 24 weeks, sitagliptin reduces the dose of insulin relative to placebo.

(2) Objective: To assess the safety and tolerability of sitagliptin.

2.1.2 Secondary

In patients with T2DM with inadequate glycemic control on insulin with or without metformin, who titrate insulin glargine (Treat-to-Target):

(1) Objective: After 24 weeks, to estimate the difference between sitagliptin and placebo on A1C.

(2) Objective: After 24 weeks, to estimate the difference between sitagliptin and placebo on fasting plasma glucose (FPG).

(3) Objective: After 24 weeks, to estimate the difference between sitagliptin and placebo on body weight.

(4) Objective: After 24 weeks, to estimate the difference between sitagliptin and placebo in the proportion of patients who achieve the fasting glucose target of 72-100 mg/dL (4.0-5.6 mmol/L).

(5) Objective: To estimate the difference between sitagliptin and placebo in the time to achieve the fasting glucose target of 72-100 mg/dL (4.0-5.6 mmol/L) for the first time.

2.2 PATIENT INCLUSION CRITERIA

All laboratory measurements must be performed **by the central laboratory** after an overnight fast ≥10 hours. A patient with screening values/findings outside ranges described in the protocol may, at the discretion of the investigator, have one repeat determination performed. If the repeat value satisfies the criterion, the patient may continue in the screening process. Only the specific out of range value/finding should be repeated (not the entire panel).

At Visit 1/Screening Visit

1. Patient has type 2 diabetes mellitus (T2DM).

2. Patient meets one of the following criteria:

   A. Patient was diagnosed with diabetes after age 40 years and insulin therapy was initiated at least 3 years after the diagnosis of diabetes,

   OR -

   B. Patient does not meet the criteria in (A) above (i.e., diagnosis < age 40 years or insulin started earlier than 3 years after diagnosis), but has a fasting C-peptide of >0.7 ng/mL.

   Note: Only patients who do not meet the criteria in (A) should have a C-peptide level measured.

3. Patient must be ≥18 and ≤80 years of age on the day of signing informed consent.

4. Patient is on a stable insulin regimen for ≥10 weeks ± metformin (immediate-release or extended-release formulation) at ≥1500 mg/day for ≥10 weeks ± sulfonylurea for ≥10 weeks, with one of the following insulins (at a dose of at least 15 U/day and a maximum dose of 150 U/day) and has a Visit 1/Screening Visit A1C ≥7.5% and ≤11.0% (for patients not on sulfonylurea) or A1C ≥7.0% and ≤10.0% (for patients on sulfonylurea):

   - Pre-mixed insulin with at least 70% basal insulin (e.g., Novolog 70/30®, Novolin 70/30®, Humalog 75/25®, or Humulin 70/30®) once-daily or twice-daily.

   - Intermediate-acting insulin (e.g., NPH/Isophane) once-daily or twice-daily.

   - Long-acting insulin (e.g., Glargine [Lantus®] and Detemir [Levemir®]) once-daily or twice-daily.

   Note: A stable insulin regimen is defined as all daily doses within 10% (or within 2 units for patient taking ≤ 20U/day) of the usual administered dose (e.g., if usual insulin dose is 50 U/day, then doses of 45-55 U/day would be considered stable).

5. Patient understands the study procedures, alternative treatments available, and risks involved with the study, and voluntarily agrees to participate by giving written informed consent. The patient may also provide consent for Future Biomedical Research. However, the patient may participate in the main trial without participating in Future Biomedical Research.

6. Patient is a male, or a female who is highly unlikely to conceive as indicated by meeting at least one of the following criteria:

A. Patient is not of reproductive potential. A female patient who is not of reproductive potential is defined as one who has either (1) reached natural menopause (defined as ≥12 months of spontaneous amenorrhea in women >45 years of age, or ≥6 months of spontaneous amenorrhea with serum FSH levels in the postmenopausal range as determined by the laboratory), or (2) had bilateral oophorectomy and/or hysterectomy, or had bilateral tubal ligation at least 6 weeks prior to screening.

B. Patient is of reproductive potential and agrees to remain abstinent or use (or have their partner use) an acceptable method of birth control within the projected duration of the study and for 14 days after the last dose of study medication. Acceptable methods of birth control are: hormonal contraception, intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, condom, vasectomy.

At Visit 4/Day 1/Randomization

7. Patient has ≥85% compliance (as measured by tablet count) with placebo treatment during run-in.

2.3 PATIENT EXCLUSION CRITERIA

All laboratory measurements must be performed **by the central laboratory** after an overnight fast ≥10 hours. A patient with screening values/findings outside ranges described in the protocol may, at the discretion of the investigator, have one repeat determination performed. If the repeat value satisfies the criterion, the patient may continue in the screening process. Only the specific out of range value/finding should be repeated (not the entire panel).

At Visit 1 / Screening Visit

Glucose Metabolism and Therapy Criteria

1. Patient has been treated with a DPP-4 inhibitor, a thiazolidinedione (TZD), or a GLP-1 mimetic or analogue, within the prior 12 weeks.

2. Patient is currently on treatment with daily use (one or more injections per day) of a pre-prandial short-acting or rapid-acting insulin (e.g., aspart, glulisine, lispro, regular insulin) alone or as part of a basal/bolus insulin regimen.

   Note: Patients using a pre-mixed insulin containing a short-acting insulin may participate.

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

4. Patient has a history of 2 or more episodes of hypoglycemia resulting in seizure, coma, or loss of consciousness, - **or** - patient has had recurrent (≥3 times per week) episodes of hypoglycemia over the past 8 weeks.

5. Patient has a history of ketoacidosis.

6. Patient is, as assessed by the investigator, not appropriate for or does not agree to target a fasting glucose of 72-100 mg/dL [4.0-5.6 mmol/L].

Patients Requiring Specific Treatments

7. Patient has a history of intolerance or hypersensitivity to sitagliptin, insulin, or metformin (if patient on metformin at Visit 1) or any contraindication to sitagliptin, insulin, or metformin (if patient on metformin at Visit 1) based upon the label of the country of the investigational site.

8. Patient is on or likely to require treatment for ≥2 consecutive weeks or repeated courses of pharmacologic doses of corticosteroids.

   Note: Inhaled, nasal, and topical corticosteroids are permitted.

9. Patient has undergone a surgical procedure within 4 weeks prior to signing informed consent or has planned major surgery during the study.

   Note: A patient who has undergone minor surgery within the prior 4 weeks and is fully recovered or a patient who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia.

10. Patient is currently participating, or has participated, in a study in which the patient received an investigational compound or used an investigational device within the prior 12 weeks of signing informed consent or is not willing to refrain from participating in another study.

    Note: A patient who has participated in a non-interventional study may be enrolled.

11. Patient is on a weight loss program and not in the maintenance phase, or has started a weight loss medication or has undergone bariatric surgery within 12 months prior to signing the informed consent.

12. Patient is currently being treated for hyperthyroidism or patient is on thyroid hormone therapy and has not been on a stable dose for at least 6 weeks.

Concomitant Disease of Organs and Systems

13. Patient has a medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C (assessed by medical history), primary biliary cirrhosis, or symptomatic gallbladder disease.

14. Patient has had new or worsening signs or symptoms of coronary heart disease or congestive heart failure within the past 3 months, or has any of the following disorders within the past 3 months:

    a. Acute coronary syndrome (e.g., MI or unstable angina)
    b. Coronary artery intervention (e.g., CABG or PTCA)
    c. Stroke or transient ischemic neurological disorder

15. Patient has a systolic blood pressure ≥160 mm Hg or a diastolic blood pressure ≥90 mm Hg and blood pressure is unlikely to be within these limits at Visit 4/Day 1 with an adjustment in antihypertensive medication.

    Note: Investigators are encouraged to maximize blood pressure control according to current guidelines. Patient may have blood pressure medication adjusted and may be enrolled if the patient's blood pressure no longer meets exclusion criteria.

16. Patient has human immunodeficiency virus (HIV) as assessed by medical history.

17. Patient has severe peripheral vascular disease (e.g., claudication with minimal activity, a non-healing ischemic ulcer, or disease which is likely to require surgery or angioplasty).

18. Patient has a clinically important hematological disorder (such as aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia).

19. Patient 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:
    • A patient with a history of malignancy >5 years prior to signing informed consent should have no evidence of residual or recurrent disease.

    • A patient with any history of melanoma, leukemia, lymphoma, or renal cell carcinoma is excluded.

Exclusion Criteria Based on Lab Abnormalities

20. Patient has exclusionary laboratory values as listed in Table 2-1.

Table 2-1

Laboratory Exclusion Criteria

Parameter[1]	Population (if applicable)	Study Limit for Exclusion
Estimated glomerular filtration rate (eGFR)[2]		<60 mL/min/1.73 m^2
Serum Creatinine (only for patients on metformin:	Male Female	≥1.4 mg/dL (124 µmol/L) ≥1.3 mg/dL (115 µmol/L)
Serum Alanine Aminotransferase (ALT)		>2.0 times Upper Limit of Normal (ULN)
Serum Aspartate Aminotransferase (AST)		>2 times ULN
Thyroid-stimulating hormone (TSH)[3]		Outside central laboratory normal range
Hemoglobin	Male Female	<12.0 g/dL (120 g/L) <11.0 g/dL (110 g/L)
Total Triglycerides (TG)[4]		>600 mg/dL (6.78 mmol/L)

[1] If screening labs are repeated, the last laboratory result should be used to assess eligibility.
[2] Calculated by the central laboratory using MDRD formula
[3] A patient excluded due to TSH criterion may be re-screened after being on a stable thyroid replacement regimen for at least 6 weeks.
[4] Patient with elevated TG may have lipid-lowering medication initiated or adjusted and continue in the study if a repeat measurement (at **Visit 3/Week -2**) no longer meets exclusion criterion. **Note**: A patient must be on stable lipid-lowering medication regimen for the 4 weeks prior to **Visit 4/Day 1**.

Other Criteria

21. Patient has a positive urine pregnancy test.

22. Patient is pregnant or breast-feeding, or is expecting to conceive or donate eggs during the study, including 14 days following the last dose of study drug.

23. Patient is, at the time of signing informed consent, a user of recreational or illicit drugs or has had a recent history of drug abuse.

    Patient routinely consumes >2 alcoholic drinks per day or >14 alcoholic drinks per week, or engages in binge drinking.

    Note: 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: 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.

24. Patient has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that

    - makes participation not in the patient's best interest,
    - might interfere with the patient's participation for the full duration of the study
    - might confound the results of the study.

25. Patient is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study.

26. Patient is currently on or likely to require treatment with a prohibited medication (see 3.2.1.2 for a list of excluded medications).

At Visit 3/Week –2

27. Patient has a clinically significant ECG abnormality during the run-in period which in the opinion of the investigator exposes the patient to risk by enrolling in the study.

28. Patient has an FPG <130 mg/dL (7.22 mmol/L) or >270 mg/dL (14.99 mmol/L).

    Note: If the patient meets the criterion of FPG >270 mg/dL (14.99 mmol/L) AND the investigator believes that an increase of the insulin glargine dose could improve glycemic control with a low risk for hypoglycemia, the patient should not be excluded at this time. The insulin glargine dose should be adjusted and the patient should start the single-blind placebo period.

29. Patient has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory abnormality, or required a new treatment or medication during the pre-randomization period which meets any previously described study exclusion criteria or which, in the opinion of the investigator, exposes the patient to risk by enrolling in the study.

At Visit 4/Day 1/Randomization

30. Patient has a site FFSG of <130 mg/dL (7.2 mmol/L) or >270 mg/dL (15.0 mmol/L).

    Note: If the patient meets this exclusion criterion AND the investigator believes that the value is not consistent with the patient's current Self-Monitoring Blood Glucose (SMBG) values and **Visit 3/Week -2** FPG value, the patient should not be excluded at this time. This visit should be changed to an **Unscheduled Visit** and the patient should be rescheduled for **Visit 4/Day 1** within 7 days. Additional single-blind placebo run-in medication should be dispensed if needed. If the patient meets this FFSG exclusion criterion at the rescheduled **Visit 4/Day1**, the patient MUST be excluded.

31. Patient has a positive urine pregnancy test.

Note: Urine pregnancy test is required to be performed before the patient is randomized.

32. Patient has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory or ECG abnormality, or required a new treatment or medication during the pre-randomization period which meets any previously described study exclusion criteria or which, in the opinion of the investigator, exposes the patient to risk by enrolling in the study.

    Note: If a patient requires initiation of a new medication at **Visit 4/Day 1**, the current visit should be changed to an **Unscheduled Visit** and the patient should be rescheduled for a **Visit 4/Day 1** to occur 1 to 2 weeks later. If needed, additional single-blind placebo run-in medication should be dispensed.

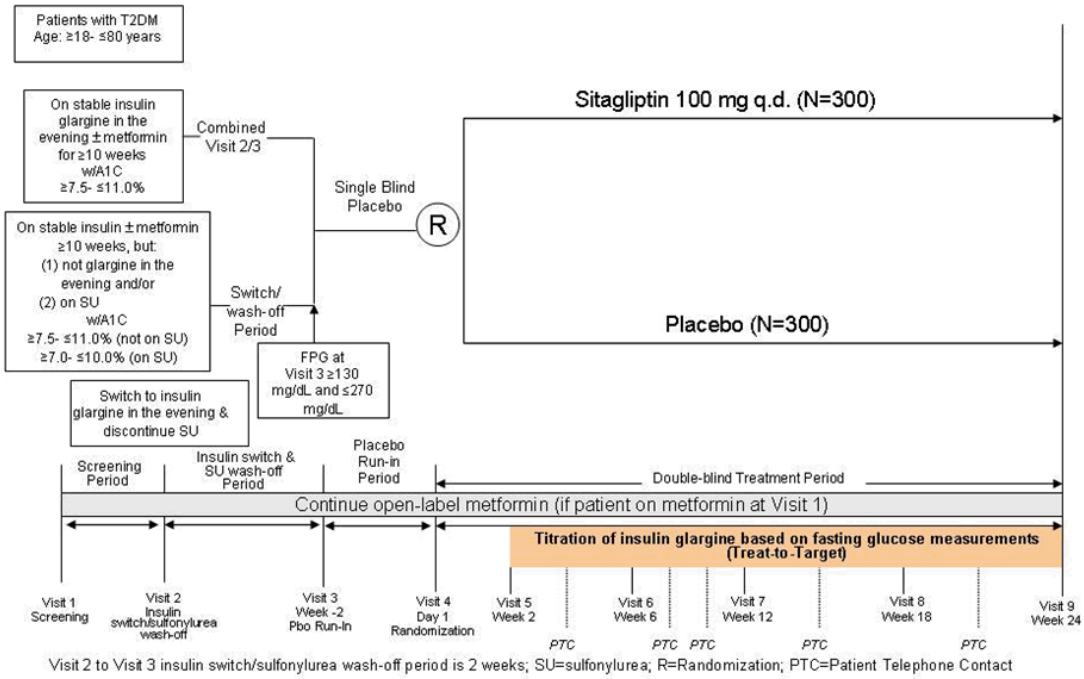
2.4 STUDY DESIGN AND DURATION

Summary of Study Design

Figure 2-1 presents an overview of the study design.

Figure 2-1

Study Design



2.4.1 Treatment Plan

See the Study Flow Chart (Section 1.7) for the timing of all procedures and laboratory samples to be done at each visit. For details regarding specific laboratories or study procedures, see Section 3.2.3.

2.4.1.1 Study Visits General Information

Fasting Prior to Scheduled Visits

Patients should be counseled to fast (i.e., no food, double-blind study medication, open-label antihyperglycemic medication [insulin, metformin and sulfonylurea], or drink except water and non-antihyperglycemic non-study medications as prescribed) for at least 10 hours prior to all study visits.

Scheduling Visits, Visit Windows, and Study Duration

At the end of each study visit, the next study visit should be scheduled. Every effort should be made to adhere to the visit schedule (refer to Study Flow Chart – Section 1.7), and generally, visits should be scheduled ± 5 days of the designated time-point. 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 double-blind study period is as close as possible to 24 weeks. If a visit is scheduled at a time other than the protocol designated time, **careful consideration must be given to the amount of study medication the patient has available**.

Visit Reminders – Telephone Contacts

Prior to each visit, patients should be contacted and reminded of:

- The date and time of appointment.
- The requirement to fast for at least 10 hours prior to the clinic visit.
- The requirement not to take insulin, metformin, sulfonylurea, and double-blind study medication at home the morning of the clinic visit.

  Note: Non-study medications that are not antihyperglycemic medications should be taken as directed by the prescribing physician.
- The requirement to measure glucose before breakfast each day.
- The requirement to bring study medication, blood glucose meter, Hypoglycemia Assessment Log (HAL), and the collected SMBG information to the clinic visit.

2.4.1.2 Visit 1/Screening Visit

At the screening visit, after informed consent is signed, patients will be assessed for **Visit 1** inclusion and exclusion criteria, have vital signs, body weight and height measured, and

will have fasting blood samples obtained. At the site's discretion, a fingerstick A1C test may be utilized to assess likelihood of meeting **Visit 1** A1C criterion. However, the fingerstick A1C measure may not be used to determine eligibility and cannot substitute for the central laboratory A1C measurement.

If the patient is not fasting at **Visit 1/Screening Visit**, a fasting lipid profile and fasting C-peptide (if required), should be obtained prior to **Visit 2** rather than at **Visit 1**. An FPG may be obtained at or prior to **Visit 2** rather than at **Visit 1**.

2.4.1.3 Visit 2

At **Visit 2**, patients will have 1) diet/exercise counseling and instructions on keeping a weight-maintenance diet throughout the study; 2) training in performing SMBG; 3) instruction on hypoglycemia symptoms, hypoglycemia management, and completion of the HAL (which will be dispensed starting at **Visit 2**).

The duration between **Visit 2 and Visit 3/Week -2** will vary based upon the patient's sulfonylurea regimen and insulin type at the **Visit 1/Screening Visit**:

- Patients *on a stable insulin glargine dose, administered once-daily in the evening ± metformin (≥1500 mg/day) for at least 10 weeks, not on a sulfonylurea and with* **A1C ≥7.5% and ≤11.0%** will go *directly* to **Visit 3/ Week -2** (since **Visit 2** is combined with Visit 3, this will be considered a **combined Visit 2/3**). Patient will start locally-sourced open-label insulin glargine at their current stable dose. Patients who have been on a stable dose of metformin at **Visit 1** will start locally-sourced open-label metformin at their current dose. If the patient requires a change in their lipid-lowering regimen **Visits 2 and 3** should not be combined and the patient should enter the run-in period. Patients should be on a stable regimen of lipid lowering medication for at least 4 weeks prior to **Visit 4/Day 1**.

- Patients *on an insulin regimen that is not insulin glargine once-daily in the evening ± metformin (≥1500 mg/day) for at least 10 weeks ± a sulfonylurea for at least 10 weeks* with **Visit 1 A1C ≥7.5% and ≤11.0% (patients not on sulfonylurea) or A1C ≥7.0% and ≤10.0% (patients on sulfonylurea),** will have a 2-week period to switch their insulin to locally-sourced open-label insulin glargine once-daily in the evening and/or to wash-off sulfonylurea prior to **Visit 3/Week -2**. Patients will be instructed to monitor their glycemic control with FFSG assessments and contact the site if the FFSG is >260 mg/dL (14.4 mmol/L) or ≤ 70 mg/dL (3.9 mmol/L). If the values are persistently over >260 mg/dL (14.4 mmol/L) or persistently ≤ 70 mg/dL (3.9 mmol/L), the site should perform an Unscheduled Visit to evaluate the continuation of the patient in the study. Otherwise, the patient can be evaluated via telephone calls.

  Note: The stable dose of metformin (immediate-release or extended-release formulation) at ≥1500 mg/day prior to **Visit 1/Screening Visit** should be maintained throughout the run-in and double-blind treatment period.

  Note: Diet/exercise therapy should be maintained throughout the entire study period.

Switch to once-daily insulin glargine at Visit 2:

All patients who are on an insulin regimen other than insulin glargine once-daily in the evening will switch to insulin glargine once-daily in the evening. The goal of this switch is to maintain the antihyperglycemic efficacy of the prior insulin regimen, but avoid an increase in the incidence of hypoglycemia. Table 2-2 provides guidance on switching patients to insulin glargine:

Table 2-2

Insulin Regimen for Switching to Insulin Glargine

Original Insulin Regimen		Switch to Glargine once-daily in the evening
Insulin Type	**Regimen**	
Glargine	Once-daily (switch only required if not dosed in the evening)	Same dose
Glargine	Twice-daily	80% of daily dose
Detemir	Once/twice-daily	70% of daily dose
NPH	Once-daily	Same dose
NPH	Twice-daily	70% of daily dose
Pre-mixed	Once-daily	Same dose
Pre-mixed	Twice-daily	70% of daily dose

For patients who experience symptomatic episodes of hypoglycemia or fingerstick glucose values ≤70 mg/dL (3.9 mmol/L) after the switch to insulin glargine once-daily in the evening at **Visit 2**, the insulin glargine dose should be reduced by the investigator according to best clinical practice. An increase of the insulin glargine dose after the switch to insulin glargine once-daily in the evening at **Visit 2** is only allowed to avoid FPG or FFSG values of >270 mg/dL (15.0 mmol/L). After a decrease or increase in the insulin glargine dose after **Visit 2**, patient should be on a stable dose for at least 1 week prior to **Visit 3/Week -2** and fingerstick glucose values and the occurrence of symptomatic hypoglycemia will continue to be monitored to further adjust the insulin glargine dose if necessary.

2.4.1.4 Visit 3/Week -2: Single-Blind Placebo Run-In Period

At **Visit 3/Week -2**, patients will be assessed to determine if they continue to meet study eligibility; eligible patients will be started on single-blind placebo to match sitagliptin 100 mg. The first dose of single-blind placebo should be taken as a witnessed dose in the clinic after completion of all **Visit 3/Week -2** study procedures. Patients will then take single-blind placebo once-daily for two weeks prior to randomization.

2.4.1.5 Visit 4/Day 1: Randomization

At **Visit 4/Day 1,** eligible patients who meet all study enrollment criteria will have all baseline laboratory tests and study procedures performed (see Study Flow Chart in Section 1.7).

Assignment of an allocation number occurs only at **Visit 4/Day 1**.

Double-blind study medication (sitagliptin 100 mg or matching placebo once daily) will be dispensed at **Visit 4/Day 1**. The first dose of double-blind study medication should be taken as a witnessed dose in the clinic after completion of all **Visit 4/Day 1** study procedures.

2.4.1.6 Visit 5/Week 2 through Visit 9/Week 24: Double-Blind Treatment Period

Patients will be dispensed one bottle of double-blind study medication at **Visit 6/Week 6, Visit 7/Week 12**, and **Visit 8/Week 18**. No study medication will be dispensed at **Visit 5/Week 2**. On the day prior to the study visits, patients should be contacted and instructed to withhold the morning dose of study medication and open-label metformin (for patients on metformin) on the day of the study visit. Patients should continue to take their non-study medications, as directed by their physician.

In addition to study visits, patients will be contacted by telephone at **Weeks 4, 8, 10, 15 and 21** to review insulin titration, monitor fingerstick glucose values (SMBG measurements), monitor the occurrence of episodes of hypoglycemia, and instruct patients on insulin dose. They will also reinforce diet/exercise and review study therapy dosing instructions.

Note: See Section 2.4.1.8 for timing of dosing of single-blind, open-label and double-blind study medication on the day of study visits.

2.4.1.7 Insulin Treat-to-Target Regimen

Starting with **Visit 5/Week 2**, but not between randomization up to **Visit 5/Week 2**, the investigator will encourage the patient to self-titrate the once-daily in the evening insulin glargine dose as appropriate to achieve glycemic control based on the treat-to-target algorithm outlined in Table 2-3 The target is a FFSG (before breakfast) or FPG (before breakfast) of 72-100 mg/dL (4.0-5.6 mmol/L).

Patients will be instructed to obtain at least one fasting fingerstick glucose measurement before breakfast daily. The investigator can instruct the patient to obtain additional measurements if she/he feels such measurements are required to monitor the glycemic control of the patient.

The titration of insulin glargine (LANTUS®) will be based on 3 consecutive measurements. Therefore titration of insulin glargine can not occur more frequently than every 3 days.

All fingerstick glucose measurements and the daily insulin glargine dose should be recorded in the Fingerstick Glucose Log.

Table 2-3

Insulin Glargine Titration based on Fasting Glucose

Fasting Glucose Measurements (before breakfast)	Change in Insulin Glargine Dose
>100 mg/dL (5.6 mmol/L) on 3 consecutive mornings	Increase dose by 2 IU
>180 mg/dL (10.0 mmol/L) on 3 consecutive mornings	Increase dose by 4 IU
≤70 mg/Dl (3.9 mmol/L) at any time	Contact study physician for insulin dose Note: If study physician cannot be reached prior to next insulin dose, reduce insulin dose by 4 IU
Goal is Fasting Glucose (before breakfast) of 72-100 mg/dL (4.0-5.6 mmol/L).	

Adherence of patients to the titration algorithm will be monitored at PTCs and scheduled visits. For patients who do not follow the insulin titration algorithm as outlined below, more frequent PTCs will be necessary to make sure that the insulin titration algorithm is closely followed by the patient.

Throughout the duration of the entire study (pre- and post-randomization), patients will be instructed to contact the site if the fingerstick glucose values are ≤70 mg/dL (3.9 mmol/L). The investigator will assess the potential need and, if necessary, extent of a reduction in the insulin glargine dose based on the details of the hypoglycemic episode (e.g. presence and absence of a trigger [e.g. skipped meal]), other FFSG/FPG values, and the current insulin dose. For discontinuation criteria based on hypoglycemia, reference Section 2.4.2.

Furthermore, in order to assess for discontinuation criteria, patients should be instructed to contact the site if the fingerstick glucose values are >270 mg/dL (15.0 mmol/L) after **Visit 4/Day 1** through **Visit 6/Week 6**, >240 mg/dL (13.3 mmol/L) after **Visit 6/Week 6** through **Visit 7/Week 12**, or >200 mg/dL (11.1 mmol/L) after **Visit 7/Week 12** through **Visit 9/Week 24**. Patients who have completed insulin titration and are on a maximally tolerated dose of insulin for at least 4 weeks with a consistent pattern of FPG greater than the relevant glycemic discontinuation threshold for the specific time point in the study (see Section 2.4.2), and **without** a reasonable explanation (e.g., intercurrent illness or medication omission), should be discontinued from the study.

2.4.1.8 Timing of Dosing of Single-Blind, Open-Label and Double-Blind Medication on Days of Study Visits

At Visit 3/Week -2:

- The **first dose** of single-blind placebo will be taken at the clinic as a witnessed dose ***after*** completion of all procedures.

At Visit 4/Day 1:

- The **first dose** of double-blind study medication will be taken at the clinic as a witnessed dose ***after*** completion of all visit procedures.

- Open-label metformin should not be taken until ***after*** completion of all visit procedures. Insulin glargine should be injected once-daily in the evening, titration of the insulin glargine dose should not start until **Visit 5/Week 2**.

At Visit 5/Week 2:

- Double-blind study medication from the bottle dispensed at **Visit 4/Day** 1 will be taken ***after*** fasting blood samples are collected.

- Open-label metformin should not be taken until ***after*** fasting blood samples are collected. Insulin glargine should be injected once-daily in the evening. Starting with this visit, the insulin glargine dose should be adjusted based on the insulin-titration algorithm (Section 2.4.1.7).

At **Visit 6/Week 6 through Visit 9/Week 24:**

- Double-blind study medication must be taken from the ***new*** study medication dispensed at these visits ***after*** fasting blood samples are collected.

- Open-label metformin should not be taken until ***after*** fasting blood samples are collected. Insulin glargine should be injected once-daily in the evening with the dose adjusted based on the insulin-titration algorithm (Section 2.4.1.7).

2.4.1.9 Post-study Telephone Follow-Up

Fourteen days after discontinuation of study medication (due to study completion or premature discontinuation from the study), the patient will be contacted by telephone to assess any serious adverse events that occurred after the administration of the last dose of study medication. This telephone inquiry will be recorded on unscheduled visit forms. If any serious adverse events require supplemental procedures, they should be performed as medically necessary.

2.4.2 Interruption of Study Medication/Discontinuation from the Study

If a patient on open-label metformin undergoes an imaging study requiring the use of **radiocontrast dye** (for example, an intravenous pyelogram or computerized tomography study with contrast) metformin should be temporarily discontinued for the time of the radiocontrast dye study. The patient's renal function should be reassessed 48 hours after the procedure. The stable dose of open-label metformin should be reinstituted after renal function has been evaluated and found not to have been reduced by the dye study. In a patient requiring an imaging study, studies not using radiocontrast dye (e.g., ultrasound-based studies, MRI with gadolinium contrast, or non-contrast CT studies) should be performed, if considered clinically appropriate, instead of radiocontrast dye studies, so as to avoid the interruption of open-label metformin.

The Sponsor should be immediately contacted when a patient is discontinued or study medication is interrupted because of an adverse event or a laboratory safety test abnormality.

Reasons for protocol-specified discontinuation from the study are listed below. All patients will be followed until resolution (i.e., return to baseline values or diagnosis determined or new stable state established, based upon investigator and Sponsor assessment) for any laboratory safety test abnormality resulting in discontinuation.

1. Informed consent withdrawn or patient requests discontinuation from the study.

2. Hypoglycemia:

   (a) Repeated (2 or more episodes since the prior study visit) FPG or fingerstick glucose <50 mg/dL (2.8 mmol/L) **with or without** symptoms of hypoglycemia, **and without** a reasonable explanation (such as increased physical activity and/or skipped meal), which persists despite progressive down-titration of insulin.

   OR -

   (b) Repeated (2 or more episodes since the prior study visit) FPG or fingerstick glucose ≤70 mg/dL (3.9 mmol/L) **with** symptoms of hypoglycemia, **and without** a reasonable explanation (such as increased physical activity and/or skipped meal), which persists despite progressive down-titration of insulin.

3. Hyperglycemia: Patients who have received insulin titration and who are on a maximally tolerated dose of insulin for at least 4 weeks with a consistent pattern of FPG greater than the relevant glycemic discontinuation threshold for the specific time point in the study (see following table), and **without** a reasonable explanation (e.g., intercurrent illness or medication omission), should be discontinued from the study.

Time in Study	Consistent FPG threshold
After **Visit 4/Day 1** through **Visit 6/Week 6**	>270 mg/dL (14.99 mmol/L)
After **Visit 6/Week 6** through **Visit 7/Week 12**	>240 mg/dL (13.32 mmol/L)
After **Visit 7/Week 12** through **Visit 9/Week 24**	>200 mg/dL (11.10 mmol/L)

Note: A consistent value is defined as repeat measurement performed within 3 to 7 days of receiving the initial report from the central laboratory. Site should reinforce diet/exercise counseling prior to repeat measurement.

4. Elevation in ALT and/or AST ≥3-times the upper limit of normal as specified in Appendix 6.3.

   OR -

   Elevations in ALT and/or AST ≥3-times the upper limit of normal with concurrent total bilirubin ≥2-times the upper limit of normal and alkaline phosphatase <2-times the upper limit of normal (see the guidance document entitled *Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials* in the Investigator Trial File Binder and refer to the ECI guidance in Section 3.4.5.2.).

5. Parameters of renal function:

   - Patient not on metformin has eGFR consistently <50 mL/min /1.73 m^2 (using the MDRD formula).

   - Patient on metformin has serum creatinine concentrations consistently ≥1.5 mg/dL (133 µmol/L) in men or ≥1.4 mg/dL (124 µmol/L) in women, **OR** eGFR consistently <60 mL/min /1.73 m^2 (using the MDRD formula) regardless of gender.

   Note: A consistent value is defined as a repeat measurement performed within 3-7 days of notification from the central laboratory.

6. Requirement for one of the excluded medications listed in Section 3.2.1.2

7. Patient develops any condition for which sitagliptin, insulin glargine, or metformin (only for patients on metformin at randomization) is contraindicated in accordance with the local drug label of the country where the patient is participating.

8. Pregnancy.

   Note: A positive urine pregnancy test requires immediate interruption of study medication until serum Beta-human chorionic gonadotrophin (β-hCG) can be

performed and found to be negative. Patient must be permanently discontinued and followed per Section 3.4.4 if pregnancy is confirmed by a positive serum pregnancy test.

9. Any medical condition or personal circumstance which, in the opinion of the investigator, exposes the patient to risk by continuing in the study or does not allow the patient to adhere to the requirements of the protocol.

If a patient discontinues study medication, he/she should complete all discontinuation visit procedures as described in Section 3.2.3.13 and listed in the Study Flow Chart (Section 1.7).

2.5 LIST OF EFFICACY MEASUREMENTS

Efficacy measurements include daily insulin dose, time when a patient meets the fasting glucose target, and laboratory assessment of A1C, FPG, and lipid panel endpoints.

2.6 LIST OF SAFETY MEASUREMENTS

Safety assessments will include collection of adverse events (including confirmed adjudicated cardiovascular serious adverse events; see Section 3.4.9), physical examination and vital signs (including PR, BP, and body weight), laboratory safety studies and locally read ECGs [redacted].

For further details refer to Section 3.4.1.

2.7 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 3.5 of the protocol details.

2.7.1 Efficacy Analyses

The primary endpoint, analysis population, and statistical method are presented in Table 2-4 below.

The primary hypothesis will be evaluated by comparing the effect of sitagliptin to placebo on the change in daily insulin dose from baseline at Week 24.

Table 2-4

Summary of Analysis Strategy for the Primary Efficacy Endpoint

Endpoint/Variable (Description, Time point)	Statistical Method	Analysis Population	Missing Data Approach
Change from baseline in daily insulin dose at Week 24	Constrained longitudinal data analysis (cLDA)	Full analysis set (FAS)	Model-based

No multiplicity adjustment is planned as there is a single primary hypothesis, consisting of a comparison of 2 treatment groups using 1 endpoint.

2.7.2 Safety Analyses

Safety analyses will be conducted in the All-Patients-as-Treated (APaT) population. Safety and tolerability will be assessed following a tiered approach by clinical review of all relevant parameters including AEs, predefined limits of change (PDLCs), laboratory tests, and vital signs. For the safety endpoint designated as Tier 1 (i.e., adverse events of symptomatic hypoglycemia), a p-value and 95% confidence interval (CI) for the between-treatment difference will be provided using the Miettinen and Nurminen method [1].

2.7.3 Power and Sample Size

This study will randomize 600 patients in a 1:1 ratio between the sitagliptin and placebo groups. It is expected that at least 95% of randomized patients, i.e., 285 patients per arm, will be eligible for inclusion in the primary analysis population. This sample size will provide 90% power (2-sided, α=0.05) to succeed in the test of the primary hypothesis based on the following assumptions: a standard deviation of 35 IU/day and the true treatment difference of 10 IU/day.

3. PROTOCOL DETAILS

3.1 RATIONALE

[redacted]

[redacted]

3.2 STUDY PROCEDURES

Refer to the Study Flow Chart in Section 1.7 for the laboratory specimens and specific procedures for each visit.

3.2.1 Concomitant and Excluded Medications/Treatments

3.2.1.1 Concomitant Medication(s)/Treatment(s)

Lipid and Blood Pressure Medications

Concurrent lipid lowering and antihypertensive medications are permitted. Patients must be on a stable lipid medication regimen for the 4 weeks prior to **Visit 4/Day 1** (refer to Section 2.3, Table 2-1). It is preferable that doses of these medications remain stable during the double-blind treatment period.

Thyroid Hormone Replacement Therapy

Patients must be on a stable dose of thyroid replacement medication (e.g., thyroxine) for at least 6 weeks prior to **Visit 1/Screening Visit**. Patients who meet the TSH exclusion criterion specified in Table 2-1 may be re-screened after being on a stable thyroid replacement regimen for at least 6 weeks.

Hormone Replacement Therapy and Birth Control Medications

Hormone replacement therapy and birth control medications are allowed, but patients should be on stable regimens, and are expected to remain on that stable regimen during the double-blind treatment period and through 14 days after the last dose of study medication.

Supplements

The use of herbal supplements and other so-called natural products should be discouraged for the duration of the study. Patients who do not discontinue the use of such supplements prior to **Visit 2** should be instructed not to change the use or dose of the supplement for the duration of the study. Patients should be instructed not to initiate new supplements for the duration of the study.

3.2.1.2 Excluded Medication(s)/Treatment(s)

Use or need for use of excluded medications will require consultation with the study investigator and the SPONSOR.

Other Antihyperglycemic Medications

Except for medications that are part of the study protocol, no other antihyperglycemic medication (such as DPP-4 inhibitors, GLP-1 analogues, sulfonylureas, meglitinides, biguanides, α-glucosidase inhibitors, PPAR-γ agonists, insulins) may be taken during the study.

Corticosteroids

The use of ≥2 consecutive weeks or repeated courses of pharmacologic doses of corticosteroids is prohibited.

Note: Inhaled, nasal, and topical corticosteroids are permitted.

Anti-Thyroid Medications

Thyroid medications to treat hyperthyroidism are prohibited.

3.2.2 Diet/Activity/Other

Diet

At **Visit 2**, the patient will receive counseling on a weight-maintaining diet consistent with the standard guidelines of the country of the investigational site (or other similar guidelines such as those from the American Diabetes Association [ADA]) from a dietitian or other qualified health professional.

The recommended diet, consistent with ADA and other standard diabetes guideline recommendations, should contain approximately 45 to 65% carbohydrate, 10 to 35% protein, and 20 to 35% fat. At each visit subsequent to **Visit 2**, patients will have monitoring and reinforcement to enhance adherence to the recommended diet regimen. **Detailed dietary information will not be captured.**

At each study visit, the patient's diet should be monitored, and counseling provided, as appropriate. Patients should be counseled to limit alcohol use to moderate amounts.

Exercise

Patients will be counseled to maintain a medically appropriate, routine exercise program; consistency in physical activity levels will be encouraged throughout the study.

3.2.3 Procedures

3.2.3.1 Self-Monitoring Blood Glucose (SMBG) Procedures

Glucose meters will be supplied to all patients at **Visit 2** in order to perform SMBG. Patients will be instructed on the procedure to perform fingerstick glucose measurements. Patients will monitor their fingerstick glucose concentrations, at least once-daily (before breakfast), but potentially more frequently at other times of the day as determined appropriate by the investigator (based upon his/her assessment of the patient's risk of increasing glucose concentrations). See further details regarding fingerstick measurements and insulin titration in Section 2.4.1.7

Throughout the duration of the entire study (pre- and post-randomization), patients will be instructed to contact the site if the fingerstick glucose values are ≤70 mg/dL (3.9 mmol/L). The investigator will assess the potential need and, if necessary, extent of a reduction in the insulin glargine dose based on the details of the hypoglycemic episode (e.g. presence and absence of a trigger [e.g. skipped meal]), other FFSG/FPG values, and the current insulin dose. For discontinuation criteria based on hypoglycemia, reference Section 2.4.2.

Furthermore, in order to assess for discontinuation criteria, patients should be instructed to contact the site if the fingerstick glucose values are >270 mg/dL (15.0 mmol/L) after Visit 4/Day 1 through Visit 6/Week 6, >240 mg/dL (13.3 mmol/L) after Visit 6/Week 6 through Visit 7/Week 12, or >200 mg/dL (11.1 mmol/L) after Visit 7/Week 12 through Visit 9/Week 24. Patients who have completed insulin titration and are on a maximally tolerated dose of insulin for at least 4 weeks with a consistent pattern of FPG greater than the relevant glycemic discontinuation threshold for the specific time point in the study (see Section 2.4.2), and **without** a reasonable explanation (e.g., intercurrent illness or medication omission), should be discontinued from the study.

3.2.3.2 Assessment and Management of Hypoglycemia

At **Visit 2**, the site will review the symptoms and management of hypoglycemia with the patient. The site will counsel the patient 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 patient 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 is obtained before or shortly (i.e., within a few minutes) after treating, the value should be recorded in the HAL. In addition, patients will be instructed to

record in the HAL any fingerstick glucose values ≤70 mg/dL (3.9 mmol/L) regardless of the presence of clinical symptoms.

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

- any episode of possible hypoglycemia resulting in symptoms,
- 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, patients 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 and recorded on the Hypoglycemia Assessment (HA) electronic case report form (eCRF). 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 HA eCRF must also be completed. Each event of symptomatic hypoglycemia must be reported as an adverse event on the adverse event 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 3.4.6.2 for guidance on reporting).

3.2.3.3 Pregnancy Testing and Contraception

Pregnancy Testing

All pre-menopausal women who are not surgically sterilized participating in the study will have a **urine** pregnancy test at each study visit indicated on the Study Flow Chart (if required by an investigational site's Institutional Review Board (IRB)/Ethics Review Committee (ERC), a serum pregnancy test can also be obtained in addition to the urine pregnancy test). A positive urine pregnancy test prior to randomization (i.e., at **Visit 1/Screening** or **Visit 4/Day 1**) requires exclusion. A positive urine pregnancy test after randomization requires immediate interruption of study medication until serum β-hCG is performed and found to be negative. Patient must be permanently discontinued and followed (see Section 3.4.4) if pregnancy is confirmed by a positive serum pregnancy test.

Contraception

Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, 2) postmenopausal, 3) not heterosexually active for the duration of this study, or 4) heterosexually active and willing to use a birth control method. The birth control method can be either a barrier method or a hormonal method to prevent pregnancy, used throughout the study starting with **Visit 1/Screening** through to 14 days after the last dose of study medication.

The following are considered adequate barrier methods of contraception: diaphragm with spermicide, condom, intrauterine device (IUD), contraceptive sponge, vasectomy, or hormonal contraception. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents). Postmenopausal is defined as ≥6 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) levels in postmenopausal range as determined by the laboratory, or ≥12 months of spontaneous amenorrhea in women >45 years of age.

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study and agree that in order to participate in the study they **must adhere to the contraception requirement (described above) for the duration of the study**. If there is any question that a patient will not reliably comply with the requirements for contraception, she should not be entered into the study.

3.2.3.4 Laboratory Monitoring

All laboratory tests outlined in the Study Flow Chart and Appendix 6.2 (e.g., FPG, A1C, CBC, chemistry panel, lipid panel, TSH, urinalysis, serum pregnancy test, etc.) will be performed by the central laboratory. Patient fingerstick glucose determinations, site fingerstick A1C, dipstick urinalysis and urine pregnancy test will be performed at the investigational site.

All laboratory testing will be performed after at least a 10-hour fast.

Laboratory test results for chemistry, hematology, urinalysis, and lipids will not be masked. FPG values will also not be masked. FPG values will be used by the investigator to monitor and guide the titration of the patient's insulin glargine dose according to the treat-to-target algorithm outlined in Section 2.4.1.7. Also, in order for the investigator to perform an evaluation for possible discontinuation from the study, the central laboratory will flag any FPG value which meets rescue or discontinuation criteria (refer to Section 2.4.2).

A1C will be masked after **Visit 4/Day 1**.

In addition to flagging FPG values meeting rescue or discontinuation criteria, the central laboratory will flag the following safety measurements meeting specific discontinuation criteria

- creatinine and/or eGFR values
- elevations ≥3-times upper limit of normal (ULN) in liver transaminases (i.e., ALT and AST) [redacted];

- elevations in ALT and/or AST ≥3-times the upper limit of normal with concurrent total bilirubin ≥2-times the upper limit of normal and alkaline phosphatase <2-times the upper limit of normal.

Refer to the Study Flow Chart (Section 1.7) for specific laboratory tests performed at each study visit.

3.2.3.5 Electrocardiogram (ECG) Procedures

At **Visit 3,** patients will have a local ECG performed. Investigators will be responsible for reviewing the ECG collected at their site to determine patient eligibility at **Visit 3** (refer to Section 2.3., Exclusion Criteria).

3.2.3.6 Anthropometric Measurements

Body weight will be measured (to be performed in duplicate) using a calibrated digital scale.

Height will be measured (to be performed in duplicate) using a site available stadiometer.

For details on measuring techniques, refer to Appendix 6.1.

3.2.3.7 Informed Consent

3.2.3.7.1 General Informed Consent

The investigator must obtain documented consent from each potential patient prior to participating in a clinical trial. Consent must be documented by the patient's dated signature or by the patient's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

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

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

3.2.3.7.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the patient, 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 patient.

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

- Blood for genomics use
- Serum and plasma for future use

3.2.3.8 Assignment of Baseline Number

A baseline number will be assigned to all screened patients upon signing the informed consent at **Visit 1/Screening Visit**. The baseline number identifies the patients for all procedures that occur prior to randomization. Each patient will be assigned only one baseline number, which is unique to an individual patient. The baseline numbers within a site must not be reused for different patients.

3.2.3.9 Stratification

Randomization will be stratified based on the patient's use of a sulfonylurea (i.e., on a sulfonylurea, or not on a sulfonylurea) and of metformin (i.e., on metformin, or not on metformin) at Visit 1/Screening Visit.

3.2.3.10 Patient Identification Cards

All patients will be given a card at **Visit 2,** identifying them as participants in a research study. The card will contain site contact information (including direct telephone numbers) to be utilized in the event of an emergency.

3.2.3.11 Randomization/Allocation

Randomization of allocation numbers will be performed via a computer-generated allocation schedule. At **Visit 4/Day 1,** through an Interactive Voice Response System (IVRS), patients will be classified among 4 strata based on the use of sulfonylurea (on or not on sulfonylurea) and the use of metformin (on or not on metformin), and then randomized to treatment group within stratum. Patients will be assigned a single allocation number which will be used to identify the patients for all procedures that occur during the double-blind treatment period (**Visit 4/Day 1** through **Visit 9/Week 24**).

A single patient/subject cannot be assigned more than 1 allocation number.

3.2.3.12 Blinding/Unblinding

Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary. Prior to unblinding, the Investigator will contact the SPONSOR. Any unblinding that occurs at the site must be documented.

3.2.3.13 Discontinuation/Withdrawal from Study

Randomized patients who discontinue due to an adverse event will have a **Discontinuation Visit** as soon as possible.

At **Discontinuation Visit**, patients will report to the clinic fasting (no food, double-blind study medication, open-label antihyperglycemic medication [insulin or metformin], or drink, except water) for at least 10 hours. Non-study medications should be taken as directed by the prescribing physician. Vital signs (pulse rate and blood pressure [measured in duplicate]) and weight (measured in duplicate) will be obtained. A physical examination will be performed. A midstream urine sample will be collected for dipstick urinalysis and blood samples will be drawn for chemistry panel, FPG, CBC, A1C and lipid panel, blood for genomics use (if the sample was not obtained previously, and the patient provided informed consent), and serum and plasma for future use (if informed consent was provided). Women of childbearing potential will have a urine pregnancy test (and serum pregnancy test if required by site's IRB/ERC). Patients with a positive urine pregnancy test will have a serum pregnancy test. Patients will also be monitored for adverse events, changes in concomitant medications and study medication compliance. A review of SMBG measurement, diet and exercise therapy, and the HAL will also be performed.

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject/patient has been discontinued/ withdrawn due to an adverse experience (telephone or FAX). When a subject/patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 3.4 SAFETY MEASUREMENTS - DETAILS.

3.2.3.14 Withdrawal From Future Biomedical Research

Patients may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Patients may withdraw consent at any time by writing to the principal investigator for the main trial. If medical records for the main trial are still available, the Investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the patient'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 patient 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 agencies to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the patient's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

3.3 EFFICACY/ MEASUREMENTS

3.3.1 Clinical and Laboratory Measurements for Efficacy

Fasting blood (at least 10 hours from the last meal/food intake/study medication intake, other than water and non-study medications) will be drawn at designated visits for efficacy parameters including A1C, FPG, and lipid panel endpoints. Daily insulin doses will be obtained from patients' self-recorded Fingerstick Glucose Log. Time when patient meets fasting glucose target will be assessed by the investigator.

3.3.2 Medication Compliance

Adherence to treatment will be assessed by patient report which may be facilitated by tablet count as outlined in the Study Flow Chart (Section 1.7). Every effort will be made to maintain adherence as close to 100% as possible. If a patient is found to have reduced compliance (<85%), site personnel should begin frequent contacts with the patient to remind the patient to take the study medication.

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical and Laboratory Measurements for Safety

Laboratory safety studies will include blood chemistry (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, alkaline phosphatase), hematology (including complete blood count [CBC], differential, absolute neutrophil count, and platelet count), urinalysis, and urine pregnancy testing (performed in women of childbearing potential). Vital signs and body weight will be collected and assessed as indicated in the Study Flow Chart (Section 1.7).

ECG will be collected and read locally. The assessment of the ECG will be the investigator's responsibility.

3.4.2 Recording Adverse Experiences

The terms "adverse experience" and "adverse event" are used interchangeably in this document.

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of

a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. 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.

Adverse experiences may occur in the course of the use of a Merck product in clinical studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal.

Adverse experiences may also occur in screened subjects/patients during any preallocation baseline period as a result of a protocol-specified intervention including washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

Such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets.

3.4.3 Definition of an Overdose for This Protocol

An overdose must be reported if any of the following occur during the conduct of the study:

1. Dosing with more than 4 tablets per day of sitagliptin (>400 mg) or matching placebo.

2. Dosing with more than 2 tablets per day of sitagliptin (>200 mg) or matching placebo for more than 28 days.

For recommended management of acute overdose, please refer to the Investigator's Brochure (IB).

Note: Any overdose meeting above criteria whether or not associated with an adverse event must be reported to headquarters' personnel within 24 hours.

Investigators/site personnel are to consult the local approved insulin glargine (LANTUS®) and metformin (XR or IR) product labels for guidance on the definition of an overdose of these agents.

3.4.3.1 Reporting of Overdose to SPONSOR

If an adverse experience(s) is associated with ("results from") the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug 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 experience must be reported within 24 hours to one of the individuals listed on the sponsor contact information page found in the Administrative Binder.

3.4.4 Reporting of Pregnancy to SPONSOR

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a subject/patient (spontaneously reported to them) which occurs during the study or within 14 days of completing the study. All subjects/patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page found in the Administrative Binder.

3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

3.4.5.1 Serious Adverse Experiences

Any serious adverse experience, including death due to any cause, which occurs to any subject/patient entered into this study or within 14 days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol, whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the contact information page.

Additionally, any serious adverse experience considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational 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 one of the individuals listed on the sponsor contact information page found in the administrative binder.

All subjects/patients with serious adverse experiences must be followed up for outcome.

3.4.5.2 Selected Nonserious Adverse Experiences

These selected non-serious adverse experiences are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Experience Case Report Forms/Worksheets.

Events of clinical interest for this trial include:

An elevated AST or ALT laboratory 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 laboratory 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 Administrative Binder, or equivalent).

3.4.6 Guidance on Adverse Events Related to Glycemia

3.4.6.1 Hyperglycemia

An adverse event of hyperglycemia requires that a patient have 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 study 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 "increased blood glucose." General guidance regarding the determination as to whether an event is considered to be an adverse event should be followed (see Section 3.4.7).

3.4.6.2 Hypoglycemia

3.4.6.2.1 Documentation

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

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

3.4.6.2.2 Guidance

All episodes considered as likely to represent symptomatic hypoglycemia by the investigator must be captured as an adverse event 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 (refer to Section 3.4.7).

3.4.7 Evaluating Adverse Experiences

Refer to Table 3-1 for instructions in evaluating adverse experiences.

Table 3-1

Evaluating Adverse Experiences

An investigator who is a qualified physician, will evaluate all adverse experiences as to:

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric studies, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric studies, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric studies, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse experience is any adverse experience occurring at any dose that:	
	†Results in death; or	
	†Is life threatening; or places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject/patient taking the product regardless of time to diagnosis); or	
	Is a cancer; or	
	Is an overdose (Whether accidental or intentional.) Any overdose whether or not associated with an adverse experience 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 experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient 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 experience. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse experience cause the test drug to be discontinued?	
Relationship to test drug	Did the test drug cause the adverse experience? The determination of the likelihood that the test drug caused the adverse experience 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 experience based upon the available information. **The following components are to be used to assess the relationship between the test drug and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test drug caused the adverse experience (AE):	
	Exposure	Is there evidence that the subject/patient was actually exposed to the test drug 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 test drug? Is the time of onset of the AE compatible with a drug-induced effect?
	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 test drug (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the dose of test drug discontinued or 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 test drug; or (3) the study is a single-dose drug study.)
	Rechallenge	Was the subject/patient reexposed to the test drug in this study? 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 study is a single-dose drug study.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST DRUG, OR IF REEXPOSURE TO THE TEST DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Study Drug Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug 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 drug relationship).**
Yes, there is a reasonable possibility of drug relationship.		There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Definitely related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
	Probably related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
No, there is not a reasonable possibility of drug relationship		Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.) **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Probably not related	There is evidence of exposure to the test drug. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The subject/patient did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

3.4.8 SPONSOR Responsibility for Reporting Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.4.9 Adjudication Procedures for Cardiovascular (CV) Events

Serious adverse events (SAEs) consistent with vascular events (cardiovascular, cerebrovascular, and peripheral vascular events) and heart failure events, revascularization procedures, and all deaths, regardless of cause, will be subject to adjudication by an expert committee external to the SPONSOR. When an eligible event is identified, the SPONSOR will request copies of additional source documentation related to the event (e.g., hospital records) from the investigator.

In some cases, it may be necessary for the investigator to request permission from the patient or his/her legally acceptable representative to obtain these documents. The investigator agrees to make every effort to obtain the necessary documentation. If any key source documents are not available, the investigator will be expected to document his/her attempts to obtain this information and to provide a narrative summarizing what is known regarding the event.

Details regarding procedures for the collection and submission of additional documentation for eligible cases can be found in separate instruction documents provided to the investigator.

3.5 STATISTICAL ANALYSIS PLAN (SAP)

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to the primary hypothesis or the statistical methods related to the primary hypothesis, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. *Post hoc e*xploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

3.5.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the SPONSOR or the designee of the SPONSOR.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, and data have been declared final and complete.

3.5.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 2.1.

3.5.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within and/or between-treatment differences are listed in Table 3-2 and Table 3-3. For endpoints other than daily insulin dose, the baseline value will be defined as the **Visit 4/Week 0/Day 1** (randomization) measurement. For daily insulin dose, the baseline value will be defined according to the rules provided in Section 3.5.3.3. If the baseline value is not available, the baseline value will be treated as missing with the exception of lipid panel endpoints, for which the last available pre-treatment value will be used.

The primary time point of the study is Week 24.

3.5.3.1 Efficacy Endpoints

The descriptions of the efficacy measurements and the time points at which they are measured are provided in Section 3.3.1 and Section 1.7 (the Study Flow Chart), respectively. The efficacy endpoints to be analyzed are listed in Table 3-2.

In describing the efficacy variables of interest below, the description is restricted to the principal time point of interest (Week 24). However, many variables will be measured at additional time points, as indicated in the Study Flow Chart (Section 1.7), and may be summarized at other time points.

3.5.3.2 Safety Endpoints

Safety endpoints include adverse events, additional hypoglycemia endpoints, percentages of patients meeting predefined limits of change (PDLC) in laboratory parameters (including blood chemistry and hematology; [redacted], and change (or percent change) from baseline at Week 24 in laboratory parameters, body weight and vital signs.

3.5.3.3 Derivation of Efficacy Endpoints

The daily insulin dose for any given week in the analysis model is defined as the average dose from the three most recent informative days preceding the date for that week. An "informative day" is defined as any day with a non-zero insulin dose, or any day on which the patient did not take insulin due to hypoglycemia or because insulin was not required to achieve the glycemic target. All other zero-dose days will be considered non-informative.

Definitions for weeks are provided in Appendix 6.5.

The A1C-to-insulin ratio at a given post-baseline time point is defined as the change from baseline in A1C (%) at the respective time point per 1 unit change in total daily dose of insulin from baseline, i.e.,

$$\text{A1C-to-insulin ratio} = \frac{\text{Change from baseline in A1C}}{\text{Change from baseline in total daily insulin dose}}$$

The total daily insulin dose used in the A1C-to-insulin ratio measurement will be the last available value preceding the A1C measurement. The derivation of daily insulin dose is the same as that used for the primary endpoint.

If the total daily dose of insulin in the above formula is zero, the ratio at the respective time point will be undefined and treated as missing.

3.5.4 Analysis Populations

3.5.4.1 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, defined separately for each analysis endpoint, consists of all randomized patients who took at least one dose of study treatment, except as follows:

- For analyses that use the constrained longitudinal data analysis (cLDA) model described in Section 3.5.5.1, the FAS population will exclude patients who did not have at least one measurement for the analysis endpoint (baseline or subsequent to the first dose of study treatment).

- For analyses that use the nonparametric analysis of covariance (ANCOVA) method, the FAS will exclude patients who did not have at least one observation for the analysis endpoint subsequent to the first dose of study treatment, or who did not have baseline data for the analysis endpoint.

- For analyses of the A1C-to-insulin ratio (which use repeated measures ANCOVA), the FAS will exclude patients who did not have baseline measurements of both A1C and insulin dose, as well as patients who did not have at least one post-baseline measurement of the A1C-to-insulin ratio.

A secondary population for analyzing key efficacy endpoints (see Table 3-2) will be the Completers population. The Completers population for the endpoints of A1C and FPG will include all patients who had a baseline measurement and a measurement at Week 24. The Completers population for the A1C-to-insulin ratio endpoint will include all patients who had baseline measurements of both A1C and insulin dose, as well as a measurement of the A1C-to-insulin ratio in the day range for Week 24. The number of patients included in the FAS and Completers populations may vary across endpoints due to the degree of missing data for each endpoint. Any substantial differences between conclusions based on the FAS population and the Completers population will be investigated.

Patients will be included in the treatment group to which they are randomized for the analysis of efficacy data. Details on the approach to handling missing data are provided in Section 3.5.5, Statistical Methods.

3.5.4.2 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized patients who received at least one dose of study treatment. Patients will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most patients this will be the treatment group to which they were randomized. Patients who took incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 3.5.5, Statistical Methods.

3.5.5 Statistical Methods

Statistical testing and inference methods for efficacy and safety analyses are described in Sections 3.5.5.1 and 3.5.5.2, respectively. All statistical tests will be conducted at α=0.05 (2-sided) level.

3.5.5.1 Statistical Methods for Efficacy Analyses

To address the primary hypothesis, the change from baseline in daily insulin dose produced by the addition of sitagliptin treatment at Week 24 will be compared to that of placebo. The difference in LS means between sitagliptin and placebo in change from baseline will be provided, along with the corresponding two-sided 95% CI and p-value. For other efficacy endpoints, only the estimate and corresponding 95% CI for the between group difference will be provided.

A constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [19] will be used as the primary analysis method. This 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. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will also adjust for the patient's use of metformin at Visit 1/Screening Visit (i.e., on metformin, or not on metformin). The treatment difference in terms of mean change from baseline to a given time point will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make proper statistical inference. Missing data are handled by the cLDA model and will not be imputed explicitly.

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different treatment groups. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and confidence intervals for individual treatment effects. Moreover, this model allows the inclusion of patients who are missing either the baseline or post-baseline measurements, thereby increasing efficiency. [redacted]

The above REML-based analysis assumes that the vector of model-based residuals follows a multivariate normal distribution. Under severe departures from normality, the REML-based analysis can be inefficient or potentially misleading. Accordingly, the residuals from the REML-based analysis, scaled by the inverse Cholesky root of the marginal variance-covariance matrix, will be subjected to a test for normality for the primary endpoint of daily insulin dose. If normality is not rejected at the α=0.001 level, then the above REML-based analysis will serve as the primary analysis. However, if normality is rejected, then the primary analysis will be conducted using multiple imputation (MI) of missing values (if any) in conjunction with a robust regression (RREG) approach that uses M-estimation. [redacted] The 0.001 level for the normality test was chosen so that the default REML-based analysis is abandoned only under a clear departure from normality; moreover, this choice guarantees that there is no material inflation in the type I error rate for the treatment effect comparison due to a potential correlation between the test statistics for the treatment effect and the normality test.

The secondary continuous efficacy endpoints (A1C and FPG) will be analyzed by the above cLDA method using data from FAS and completers populations.

Repeated measures ANCOVA (RM ANCOVA), a generalization of the standard ANCOVA to accommodate repeated measurements, will be used for analyses of the A1C-to-insulin ratio. The cLDA method will not be used for this endpoint because the ratio is not defined at baseline. With RM ANCOVA, the mean of the response is modeled as a standard ANCOVA, but there are time-specific versions of each ANCOVA term at each week and a correlation structure among the post-baseline time points to acknowledge the repeated nature of the measurements. [redacted] If normality of the residuals from this RM ANCOVA model is rejected at the α=0.001 level, the MI→RREG method described above will be used in lieu of RM ANCOVA.

All lipid panel endpoints except for triglycerides will be analyzed by the above cLDA method. Triglycerides will be analyzed using a nonparametric method: an ANCOVA based upon Tukey's normalized ranks on the change from baseline [20]. This model will

have the terms of treatment, baseline value, and the patient's use of metformin at Visit 1/Screening Visit. For this analysis, within-treatment effects will be estimated using medians, and between-treatment effects will be estimated using the Hodges-Lehmann estimate [21] with a corresponding distribution-free 95% confidence interval (CI) based on Wilcoxon's rank sum test. The standard deviation of the median will be computed as (Q3-Q1)/1.075, where Q3 and Q1 represent the 75th and 25th percentiles, respectively. Missing values will be imputed from the last observed post-baseline measurement, if available.

An analysis of the first time to achieve the fasting glucose target of 72-100 mg/dL (4.0-5.6 mmol/L) after randomization, i.e., a time-to-target analysis will be performed. The proportion of patients achieving the fasting glucose target of 72-100 mg/dL in each treatment group will be summarized. The Kaplan-Meier estimates (and 95% CI) at Week 24 within each treatment group as well as the between-group difference at Week 24 will be provided. Plots of the Kaplan-Meier estimate of the distribution of the time-to-target will be provided for each treatment arm.

The analyses of the proportions of patients achieving the fasting glucose target of 72-100 mg/dL (4.0-5.6 mmol/L) at Week 24 or at the last visit if a patient discontinued before Week 24 will be conducted using the M&N method, an unconditional, asymptotic method. The analysis will be stratified by the patient's use of metformin at Visit 1/Screening Visit. The differences in proportions, along with the corresponding 95% CIs will be calculated. The analysis will be conducted using data from the FAS population.

Table 3-2 summarizes the analysis strategy for all efficacy endpoints. The strategy to address multiplicity issues with regard to multiple endpoints is described in Section 3.5.6, Multiplicity.

Table 3-2

Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time Point)	Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Change from baseline in daily Insulin dose at Week 24	P S	cLDA cLDA	FAS Completers	Model-based N/A
Secondary				
Change from baseline in A1C at Week 24	P S	cLDA cLDA	FAS Completers	Model-based N/A
Change from baseline in FPG at Week 24	P S	cLDA cLDA	FAS Completers	Model-based N/A
Time to target	P	Kaplan-Meier	FAS	N/A
Percent of patients achieving fasting glucose target	P	M&N	FAS	N/A
Other				
A1C-to-insulin ratio	P S	RM ANCOVA RM ANCOVA	FAS Completers	Model-based N/A
Percent change from baseline in Total cholesterol, LDL-C, HDL-C, or non-HDLC at Week 24	P	cLDA	FAS	Model-based
Percent change from baseline in TGs at Week	P	Nonparametric ANCOVA	FAS	LOCF
†P=Primary; S=Secondary.				

3.5.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, vital signs, and body weight measurements.

The analysis of safety results will follow a tiered approach (Table 3-3). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of special 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. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

For this study, there is a single Tier 1 safety endpoint: adverse events of symptomatic hypoglycemia. Adverse events (summary measures, specific terms, system organ class terms, and specific, confirmed adjudicated cardiovascular serious adverse events) and PDLC in laboratory parameters that are not pre-specified as endpoints of special interest will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events

observed. Membership in Tier 2 requires that at least 4 patients in any treatment group exhibit the event or meet the PDLC criterion. All other adverse events and PDLC will belong to Tier 3.

The threshold of at least 4 patients with 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 patients with 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 CI should be regarded as a helpful descriptive measure to be used in review, and not as a formal method for assessing the statistical significance of the between-group differences in adverse events and PDLC.

The continuous endpoint of body weight will be considered Tier 2 safety parameter. Changes from baseline in laboratory measurements and vital signs will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided in table format. Mean change from baseline over time will be plotted with the corresponding standard errors. For safety endpoints, all analyses will be based on the observed data (i.e., with no imputation of missing data).

Table 3-3 summarizes the analysis strategy for safety endpoints. For safety events, p-values (Tier 1 only) and 95% CIs (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with event; the analyses will be performed using the M&N method. For the analysis of change from baseline in body weight, the same cLDA model as for efficacy endpoints will be used to give the confidence intervals on between-group differences.

Table 3-3
Analysis Strategy for Safety Parameters

Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Any AE of symptomatic hypoglycemia	X	X	X
Tier 2[1]	AE summary measures		X	X
	Specific AEs[2], SOCs, specific confirmed CV SAEs, and PDLCs		X	X
	Any AE of hypoglycemia		X	X
	AEs of severe hypoglycemia		X	X
	Any			
	Requiring medical assistance			
	Not requiring medical assistance			
	Body weight change from baseline at Week 24		X	X
Tier 3	All endpoints listed as Tier 2 (above) that have incidence <4 patients in both treatment groups			X
	Additional hypoglycemia adverse event endpoints			X
	Change from baseline results (laboratory measurements and vital signs)			X

[1] Endpoints listed here will qualify for Tier 2 only if the incidence is ≥4 patients in at least one of the treatment groups except for the continuous endpoint of body weight, which is considered Tier 2 safety parameter.
[2] Among those endpoints not pre-specified as Tier 1.
SAE=Serious adverse event; SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

Analysis of Hypoglycemia

The Tier 1 analysis for hypoglycemia will include the numbers and percentages of patients 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 patients experiencing one or more of each the following, regardless of glucose value:

- Adverse events of hypoglycemia (symptomatic or asymptomatic)
- 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. 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 patients with each of the following, overall and by lowest reported glucose category (<50 mg/dL [2.78 mmol/L], ≤70 mg/dL [3.89 mmol/L], >70 mg/dL [3.89 mmol/L], or unknown). A patient's lowest glucose category will be classified as unknown only if no glucose measurements are available for that patient.

    1. any episodes (symptomatic or asymptomatic)
    2. symptomatic episodes
    3. asymptomatic episodes

- The numbers and percentages of patients with episodes having precipitating factors, overall and separately by factor
- The number of episodes per patient
- The number of each of the following (summed across all patients). 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

A summary of patients with episodes that were reported on the HA eCRF but were not classified by the investigator as adverse events will also be provided. If a substantial number of patients 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.

3.5.5.3 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 hypothesis tests will be performed on these characteristics. The number of patients enrolled in the study by investigator and treatment group will be tabulated. The number and percentage of patients screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Primary and secondary diagnoses, and prior and concomitant therapies, will be summarized by treatment group. 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, standard deviation [SD], median, range and proportion will be provided

- Continuous baseline demographic variables: age (years), weight (kg), and BMI (kg/m^2).
- Categorical baseline demographic variables: gender (male, female), race (White, Black, Asian or Other), and ethnicity (Hispanic/Latino or not).
- Baseline A1C, and distribution of A1C at baseline (A1C levels <8.0%, ≥8.0% to <9.0%, ≥9.0% to <10.0%, ≥10.0%).
- Baseline FPG.
- Duration of diabetes mellitus (years).
- Baseline insulin dose
- Prior diabetes pharmacotherapy at **Visit 1/Screening**

    1. the patient's use of sulfonylurea: on or not on sulfonylurea
    2. the patient's use of metformin: on or not on metformin

3.5.6 Multiplicity

There is a single efficacy hypothesis in this trial, consisting of a comparison of 2 treatment arms using one endpoint. No between-group comparisons will be tested for other efficacy endpoints. Therefore, no multiplicity adjustment is necessary to control the overall Type I error at 0.05 (2-sided) for efficacy hypotheses.

From a safety standpoint, application of a multiplicity adjustment could potentially mask a safety concern. Thus, no control of Type I error rate beyond the per-comparison α=0.05 nominal level will be applied to the safety analyses, with the realization that spurious statistical significance may be observed for some endpoints.

3.5.7 Sample Size and Power Calculations

3.5.7.1 Sample Size and Power for Efficacy Analyses

This study will randomize approximately 600 patients in a 1:1 ratio between the sitagliptin and placebo groups. It is expected that at least 285 patients per group will be eligible for inclusion in the primary analysis population.

With respect to the assessment of the primary efficacy endpoint of daily insulin dose change from baseline at Week 24, Table 3-4 shows the between-group differences that can be detected with 80% and 90% power for three standard deviation assumptions using α=0.05 (two-sided) based on the t-test.

Table 3-4

Power Calculation for the Primary Efficacy Hypothesis
285 Evaluable Patients per Group and α=0.05 (two-sided)

Endpoint	SD† (IU/day)	Minimum Detectable Difference (IU/day)	
		80% Power	90% Power
Daily insulin dose change from baseline at Week 24	25	5.9	6.8
	30	7.1	8.2
	35	8.2	9.5
†Assumed based on references [14], [22], [23]			

3.5.7.2 Sample Size and Power for Safety Analyses

If no adverse events are observed in a treatment group in which 300 patients are enrolled, the upper bound of the 95% CI for the within-group incidence rate will be 1.2%.

3.5.8 Subgroup Analyses and Effect of Baseline Factors

No subgroup analyses are planned for this study.

3.5.9 Interim Analyses

No interim analyses are planned for this study.

3.5.10 Compliance (Medication Adherence)

For the summary of patient compliance with blinded study medication, a day within the Double-blind Treatment Period will be considered a compliant day if the patient took exactly 1 tablet of study medication (sitagliptin or matching placebo) from the correct bottle.

For a patient who is followed for the entire study period, the "Number of Days in Double-blind Treatment Period" is the total number of days from the first dose of study medication to the last scheduled day for treatment administration for that patient. For a patient who discontinues from the study prematurely, the "Number of Days in Double-blind Treatment Period" is the total number of days from the first dose of study medication to the date of the last dose of study medication. For each patient, percent compliance will then be calculated using the following formula:

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

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

3.5.11 Extent of Exposure

The extent of exposure to sitagliptin or matching placebo will be evaluated by summary statistics and frequencies for the "Number of Days on Therapy" by treatment group. The extent of exposure to any insulin dose will also be summarized.

3.6 PACKAGING, LABELING, STORAGE, AND RETURN OF CLINICAL SUPPLIES

3.6.1 Product Descriptions

Investigational materials will be provided by the SPONSOR as summarized in the Table 3-5.

Table 3-5

Product Descriptions

Product Name & Potency	Dosage Form
Sitagliptin Phosphate 100 mg	Tablet
Placebo to match Sitagliptin Phosphate 100 mg	Tablet

Other clinical supplies, insulin and metformin will be supplied locally, as needed. The investigator or designee will record the lot number, expiration date, and drug dispensed.

3.6.2 Packaging Information

Patients will receive blinded bottles at Visits 3, 4, 6, 7 and 8. **No kitting required**.

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

3.6.3 Clinical Supplies Disclosure

The IVRS should be used in order to unblind patients and to unmask drug identity. The SPONSOR will not provide disclosure envelopes with the clinical supplies. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary. Prior to unblinding, the investigator will attempt to contact the CRA. Any unblinding that occurs at the site must be documented.

3.6.4 Storage and Handling Requirements

The storage conditions will be indicated on the label.

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range as specified on the

label or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

3.6.5 Standard Policies / Return of Clinical Supplies

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount dispensed to and returned by the patients, and the amount remaining at the conclusion of the study. In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel if directly handling tablets or capsules that are returned (i.e., when counting returns). The CRA should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as indicated on the Contact Information page(s).

U.S. sites should follow instructions for the Clinical Supplies Return Form and contact your SPONSOR representative for review of shipment and form before shipping.

For sites outside of the United States, the local country SPONSOR personnel will provide appropriate documentation that needs to be completed for drug accountability.

The investigator or designated assistant should not open individual clinical supply containers and count tablets before dispensing to the patients. Any deviation from this must be discussed with the CRA.

3.6.6 Distributing to Sites and Dispensing to Patients

Study personnel will have access to Interactive Voice Response System (IVRS) to allocate patients, to assign drug to patients 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.

3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens for this protocol will be provided by the SPONSOR.

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

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, 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 study 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.

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time (“HIPAA”).

4.1.3 Confidentiality of Investigator Information

For All Studies

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site

personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- 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 agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

For Multicenter Studies
In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; 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 study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/ Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study, provide all data, and upon completion or termination of the clinical study submit any

other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. 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 study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) 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.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this SPONSOR's studies. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study 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 site's IRB/IEC.

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written 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 study.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, http://clinicaltrials.gov/. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

4.6 PUBLICATIONS

This study 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 study results within 12 months after the last data become available, which may take up to several months after the last patient visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC studies. For studies intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the study results until the SPONSOR notifies the investigator that all relevant regulatory requirements on the study drug have been fulfilled with regard to pediatric-related regulatory filings. Merck will post a synopsis of study results for approved products on www.clinicalstudyresults.org and www.clinicaltrials.gov by 12 months after the last patient's last visit or within 7 days of product approval in any major markets (United States, Europe or Japan), 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.

For multicenter studies, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicalstudyresults.org if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single site data prior to the main paper may be of value. Limitations of single 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 should meet conditions 1, 2, and 3. Significant contributions to study 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 study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible to defend 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 study 60 days prior to submission for publication/ presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication timelines.

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8. SIGNATURES

8.1 SPONSOR'S REPRESENTATIVE

TYPED NAME	SIGNATURE	DATE

8.2 INVESTIGATOR

I agree to conduct this clinical study 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); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study 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 experiences as defined in the SAFETY MEASUREMENTS section of this protocol. 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 study 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	SIGNATURE	DATE