Official Protocol Title:	A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of the Continuation of Sitagliptin Compared with the Withdrawal of Sitagliptin During Initiation and Titration of Insulin Glargine (LANTUS®) in Subjects with Type 2 Diabetes Mellitus
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TITLE:

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of the Continuation of Sitagliptin Compared with the Withdrawal of Sitagliptin During Initiation and Titration of Insulin Glargine (LANTUS®) in Subjects with Type 2 Diabetes Mellitus

IND NUMBER: 65,495
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2; 5.2.2	Trial Treatment; Timing of Dose Administration	Table 3 Metformin BID dosing was removed and the text was updated to allow the dose frequency to be defined by local labels or clinical practice guidelines.	Updated to account for the differences in dose frequency across countries.
5.5.3 6	Excluded Medications/Treatments Applicable to Only CGM Subjects; Study Flow Chart, Footnote O	Added text and footnote to state that subjects participating in the CGM sub-study cannot use acetaminophen and/or medications containing acetaminophen for at least 24 hours prior to sensor insertion and while the sensor is being used.	Acetaminophen interferes with the signal from the CGM sensor used in the trial and can potentially give falsely high readings.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
2.1	Trial Design	Added text to clarify that the interval between Visit 1 and either the combined Visit 2/3/4, or Visit 2, can be no more than 2 weeks.	Updated to correct a typographical error and revise allowed timeframe between Visit 1 and Visit 2 or combined Visit 2/3/4.
2.1	Trial Design	Table 1 Clarified pre-randomization procedures	Updated to clarify the pre-randomization management of subjects.
3.1 3.2	Primary Objectives and Hypotheses; Secondary Objectives and Hypotheses	Changed ≤3.9 mmol/mol to ≤3.9 mmol/L in four of the objectives/hypotheses.	Updated to correct a typographical error.
4.1	Background	Added text to clarify that the Investigator Brochure (IB) should be referenced for additional information on sitagliptin, including the Reference Safety Information (RSI).	Updated to clarify the source for the Reference Safety Information (RSI).
5.1.2	Subject Inclusion Criteria	Criteria #5: For subjects who qualify for the combined visit, the Screening Visit A1C value can be used to assess eligibility as long as the value was measured within 2 weeks, as opposed to 3 weeks, of the combined visit.	Updated to correct a typographical error.

5.1.3 5.5.1 6	Subject Exclusion Criteria (Table 2); Allowed Medication; Study Flow Chart-Footnote V	Defined criteria for when subjects with elevated triglyceride (TG) levels, must be re-screened after being on a lipid-lowering regimen, as opposed to continuing in the trial.	Updated to ensure patients are on a stable lipid-lowering regimen for specified amount of time prior to randomization.
5.2	Trial Treatment	Added text to clarify that if on metformin, another DPP-4 inhibitor and a sulfonylurea, eligible subjects will discontinue the sulfonylurea and switch their other DPP-4i to sitagliptin 100 mg at Visit 2.	Added text to clarify the management of subjects at Run-in.
5.2.1.2	Dose Modification of Sitagliptin/Matching Placebo to Sitagliptin	Added text to state that the dose of sitagliptin or matching placebo cannot be modified throughout the 30-week double-blind treatment period. If a subject is suspected of having pancreatitis, study medications should be interrupted; study medications may be re-initiated if pancreatitis is not confirmed.	Added to clarify the dose cannot be modified and the actions required with study medication if pancreatitis is suspected.
5.2.1.2	Dose Modification (Titration) of Insulin Glargine (LANTUS®)	Table 4 Corrected, >140 mg/dL is equivalent to >7.8 mmol/L not 10 mmol/L.	Updated to correct a typographical error.

5.5	Concomitant Medications/ Vaccinations (Allowed and Prohibited)	.Any medications taken by the subject within 15 weeks of Visit 1/Screening, including AHA medications, should be recorded on the appropriate electronic case report form (eCRF).	Updated to correct the length of time, prior to Visit 1, for which subjects must documents **all** medications.
5.5.1 6	Allowed Medications; Study Flow Chart-Footnote J	Defined criteria for when subjects with elevated blood pressure, must be re-screened after being on a blood pressure-lowering regimen, as opposed to continuing in the trial.	Updated to ensure patients are on a stable blood pressure-lowering regimen for specified amount of time prior to randomization.
5.5.2	Excluded Medication(s)/Treatment(s)	Added the following: Rapid- and intermediate- acting insulin and other basal insulins should not be taken during the trial.	To clarify that only LANTUS® can be taken during this trial.
5.8.1.2	Discontinuation from Blinded Study Therapy	Removed statement that subjects who continue to participate in the trial off of study medication are responsible for procurement of AHA background therapy.	The sponsor will not cover the cost of non-study medications, but will cover the cost of metformin and LANTUS®.
6	Study Flow chart	Increased the visit window between Visit 4 and Visit 5 to 7 days.	Updated to Allow sites and subjects a little more flexibility

7.1.1.8	Trial Compliance (Medication/Diet/Activity/Other)	Added the following: LANTUS® will be administered by the subject in the evening and the site will call the subject on Day 2 to record the dose and timing of administration.	To clarify that LANTUS® dose administration cannot be witnessed at site on Day 1, but that the site will contact the subject the next day for follow-up.

1.0 TRIAL SUMMARY

Abbreviated Title	Randomized Sitagliptin Withdrawal Study
Trial Phase	Phase III
Clinical Indication	Treatment of Type 2 Diabetes Mellitus (T2DM)
Trial Type	Interventional
Type of control	Placebo
Route of administration	Oral
Trial Blinding	Double-blind
(Select Groups)	Treatment Groups: Sitagliptin 100 mg Sitagliptin-matching Placebo
Number of trial subjects	Approximately 700 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 94 weeks from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 34-42 weeks from the time Informed Consent Form (ICF) is signed through the final contact, dependent upon the subject's AHA treatment at study entry.
Randomization Ratio	1:1

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled trial of continuing sitagliptin versus withdrawing sitagliptin in subjects with type 2 diabetes mellitus (T2DM) and inadequate glycemic control who initiate and titrate insulin glargine (LANTUS®) based on a treat-to-target algorithm to achieve fasting glucose levels of 72-100 mg/dL (4-5.6 mmol/L). This trial will be conducted in conformance with Good Clinical Practices.

The duration of the trial (from Visit 1 to the post-treatment telephone contact) will be between approximately 34 and 42 weeks (with up to 9 scheduled clinic visits), depending upon the subject's AHA treatment at screening. This will include the following:

- Screening Period:
    - For subjects eligible for a combined Visit 2/3/4, the interval between Visit 1 and Visit 2/3/4 should be no more than 2 weeks.
    - For all other subjects, the interval between Visit 1 and Visit 2 should be no more than 2 weeks

- Pre-Randomization Period:
    - For subjects who are on metformin + sitagliptin at screening, **no** pre-randomization period is required; these patients will be randomized at a combined Visit 2/3/4.
    - For subjects taking metformin + a DPP-4 inhibitor other than sitagliptin, ± a sulfonylurea at screening, a **4-week** pre-randomization period for sitagliptin initiation and dose stabilization AND/OR for sulfonylurea wash-off beginning at Visit 2 (Visit 2 to Visit 4);
    - For subjects taking metformin + sulfonylurea at screening, an **8-week** pre-randomization period for switching subjects from the sulfonylurea to sitagliptin at Visit 2 (Visit 2 to Visit 4);
- Treatment Period: All subjects will have a **30-week** double-blind, placebo-controlled treatment period (Visit 4 to Visit 9) including telephone contacts at Weeks 1, 2, 4, 8, 10, 15, 21, and 27;
- Post-treatment Telephone Contact: All subjects will receive a telephone call **14 days** after the last dose of blinded study drug.

Management of Subjects Prior to Randomization

Refer to Table 1 below for a summary of pre-randomization requirements and management based upon the subject's background therapy.

Table 1 Management of Subjects Prior to Randomization

Treatment Regimen at Screening (Visit 1)	Visit 1 A1C Requirement	Visit 2 Procedure	Visit 3 (Week -1) A1C Requirement	Visit 4 Procedure (1 week after Visit 3)
Stable dose of Met IR or XR (≥1500 mg/day) and sita (100 mg/day) administered separately for ≥12 weeks	7.5% to 11.0% (58 to 97 mmol/mol)	*Go to combined Visit 2/3/4* → (Screening A1C to assess eligibility)		*Combined Visit 2/3/4 (occurs ≤ 2 weeks after Visit 1):* • Continue Met* • Randomization (start DB therapy, i.e., continue sita or withdraw sita/initiate sita placebo) • Initiate Insulin Glargine
Stable dose of Met (≥1500 mg/day) and sita (100 mg/day) in a FDC for ≥12 weeks	7.5% to 11.0% (58 to 97 mmol/mol)	*Go to combined Visit 2/3/4* → (Screening A1C to assess eligibility)		*Combined Visit 2/3/4 (occurs ≤ 2 weeks after Visit 1)::* • Stop FDC • Initiate Met* (IR or XR) at same dose as in FDC • Randomization (start DB therapy, i.e., continue sita or withdraw sita/initiate sita placebo) • Initiate Insulin Glargine
Stable dose of Met IR or XR (≥1500 mg/day) and sita (100 mg/day) administered separately + SU for ≥12 weeks	7.0% to 10.0% (53 to 86 mmol/mol)	Instruct subjects to: • Stop SU (**SU wash-off**) • Continue Met* • Continue sita (100 mg/day)	7.5% to 11.0% (58 to 97 mmol/mol)	• Continue Met* • Randomization (start DB therapy, i.e., continue sita or withdraw sita/initiate sita placebo) • Initiate Insulin Glargine
Stable dose of Met (≥1500 mg/day) and sita (100 mg/day) in a FDC + SU for ≥12 weeks	7.0% to 10.0% (53 to 86 mmol/mol)	Instruct subjects to: • Stop SU (**SU wash-off**) • Continue Met and sita FDC	7.5% to 11.0% (58 to 97 mmol/mol)	• Stop FDC • Initiate Met* (IR or XR) at same dose as in FDC • Randomization (start DB therapy, i.e., continue sita or withdraw sita/initiate sita placebo) • Initiate Insulin Glargine

Treatment Regimen at Screening (Visit 1)	Visit 1 A1C Requirement	Visit 2 Procedure	Visit 3 (Week -1) A1C Requirement	Visit 4 Procedure (1 week after Visit 3)
Stable dose of Met IR or XR (≥1500 mg/day) and SU in a FDC + sita (100 mg/day) for ≥12 weeks	7.0% to 10.0% (53 to 86 mmol/mol)	Instruct subjects to: • Stop FDC (**SU wash-off**) • Initiate Met* (IR or XR) at same dose as in FDC • Continue sita (100 mg/day)	7.5% to 11.0% (58 to 97 mmol/mol)	• Continue Met* • Randomization (start DB therapy, i.e., continue sita or withdraw sita/initiate sita placebo) • Initiate Insulin Glargine
Stable dose of Met IR or XR (≥1500 mg/day) and DPP-4i other than sita administered separately or in a FDC for ≥12 weeks	7.5% to 11.0% (58 to 97 mmol/mol)	Instruct subjects to: If not on FDC • Continue Met* • Switch to sita (100 mg/day) If on FDC • Stop FDC • Initiate Met* (IR or XR) at same dose as in FDC • Switch to sita (100 mg/day)	7.5% to 11.0% (58 to 97 mmol/mol)	• Continue Met* • Randomization (start DB therapy, i.e., continue sita or withdraw sita/initiate sita placebo) • Initiate Insulin Glargine
Stable dose of Met IR or XR (≥1500 mg/day) and DPP-4i other than sita administered separately or in a FDC + SU for ≥12 weeks	7.0% to 10.0% (53 to 86 mmol/mol)	Instruct subjects to: If not on FDC • Stop SU (**SU wash-off**) • Continue Met* • Switch to sita (100 mg/day) If on FDC • Stop SU (**SU wash-off**) • Stop FDC • Initiate Met* (IR or XR) at same dose as in FDC • Switch to sita (100 mg/day)	7.5% to 11.0% (58 to 97 mmol/mol)	• Continue Met* • Randomization (start DB therapy, i.e., continue sita or withdraw sita/initiate sita placebo) • Initiate Insulin Glargine

Treatment Regimen at Screening (Visit 1)	Visit 1 A1C Requirement	Visit 2 Procedure	Visit 3 (Week -1) A1C Requirement	Visit 4 Procedure (1 week after Visit 3)
Stable dose of Met IR or XR (≥1500 mg/day) and SU in a FDC + DPP-4i other than sita for ≥12 weeks	7.0% to 10.0% (53 to 86 mmol/mol)	Instruct subjects to: • Stop FDC (**SU wash-off**) • Initate Met* (IR or XR) at same dose as in FDC • Switch to sita (100 mg/day)	7.5% to 11.0% (58 to 97 mmol/mol)	• Continue Met* • Randomization (start DB therapy, i.e., continue sita or withdraw sita/initiate sita placebo) • Initiate Insulin Glargine
Stable dose of Met IR or XR (≥1500 mg/day) and SU administered separately or in a FDC for ≥12 weeks	7.5% to 11.0% (58 to 97 mmol/mol)	Instruct subjects to: <u>If not on FDC</u> • Continue Met* • Stop SU and initiate sita (100 mg/day) **(SU switch)** <u>If on FDC</u> • Stop FDC (**SU wash-off**) • Initiate Met* (IR or XR) at same dose as in FDC • Initiate sita (100 mg/day) **(SU switch)**	7.5% to 11.0% (58 to 97 mmol/mol)	• Continue Met* • Randomization (start DB therapy, i.e., continue sita or withdraw sita/initiate sita placebo) • Initiate Insulin Glargine

Sita: sitagliptin; Met: metformin; IR: Immediate Release; XR: Extended Release; DB: double-blind; SU: Sulfonylurea; FDC: Fixed-Dose Combination; DPP-4i: DPP-4 inhibitor
*Continue on same metformin as at enrollment – IR or XR
Acceptable doses of DPP-4is:

- Saxagliptin 5 mg od
- Linagliptin 5 mg od
- Alogliptin 25 mg od
- Vildagliptin 50 mg bid

Management of Randomized Subjects

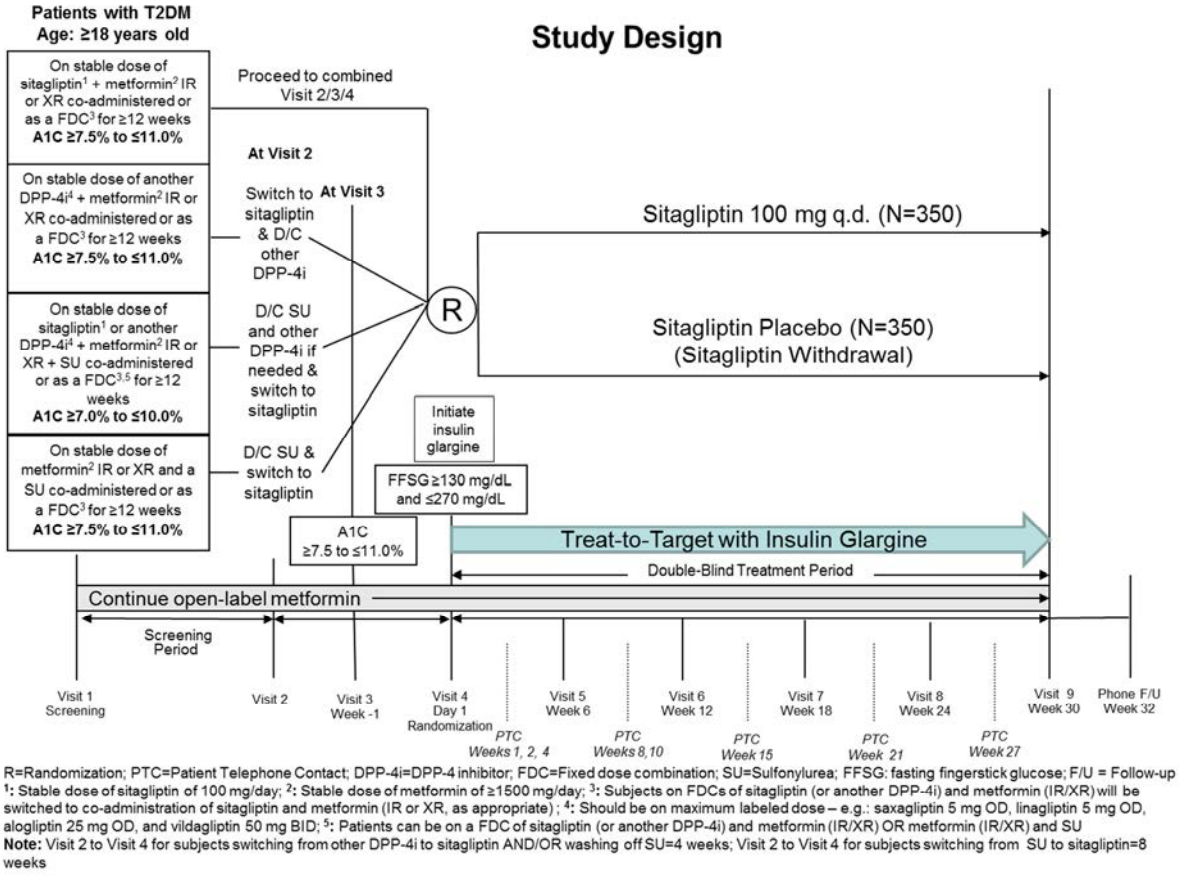
At either the combined Visit 2/3/4 (Randomization/Day 1) or Visit 4 (Randomization/Day 1), as applicable, subjects will be randomized in a 1:1 ratio to either sitagliptin 100 mg daily or sitagliptin-matching placebo daily and enter the 30-week, double-blind, placebo-controlled treatment period. Insulin glargine (LANTUS®) will be initiated at 10 units daily administered in the evening and titrated based on a treat-to-target algorithm (see Section 5.2.1.2) to achieve fasting glucose levels of 72-100 mg/dL (4.0-5.6 mmol/L). Subjects are to remain on their stable dose of metformin (≥1500 mg/day) while receiving blinded study drug during the double-blind treatment period.

Every appropriate effort should be made to support subject study completion on the anti-hyperglycemic agent (AHA) regimen to which they are randomized. Subjects may discontinue blinded study therapy without withdrawing consent. These subjects should complete procedures for the Discontinuation Visit (when they discontinue blinded study therapy), and should be requested to return to the study site for all scheduled visits for safety and efficacy evaluations. If they are unwilling to do so, alternative efforts should be made to collect safety and efficacy information as summarized in Sections 5.8.1 and 7.1.4. Withdrawal of consent will result in discontinuation of all study procedures. Subjects withdrawing consent should be encouraged to complete procedures for the Discontinuation Visit followed by a post-treatment telephone call 14 days after the last dose of blinded study drug. The purpose of the 14-day post-treatment telephone call is to collect information about the subject's health status (e.g., evaluate if the subject experienced any SAEs).

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.



R=Randomization; PTC=Patient Telephone Contact; DPP-4i=DPP-4 inhibitor; FDC=Fixed dose combination; SU=Sulfonylurea; FFSG: fasting fingerstick glucose; F/U = Follow-up
[1]: Stable dose of sitagliptin of 100 mg/day; [2]: Stable dose of metformin of ≥1500 mg/day; [3]: Subjects on FDCs of sitagliptin (or another DPP-4i) and metformin (IR/XR) will be switched to co-administration of sitagliptin and metformin (IR or XR, as appropriate) ; [4]: Should be on maximum labeled dose – e.g.: saxagliptin 5 mg OD, linagliptin 5 mg OD, alogliptin 25 mg OD, and vildagliptin 50 mg BID; [5]: Patients can be on a FDC of sitagliptin (or another DPP-4i) and metformin (IR/XR) OR metformin (IR/XR) and SU
Note: Visit 2 to Visit 4 for subjects switching from other DPP-4i to sitagliptin AND/OR washing off SU=4 weeks; Visit 2 to Visit 4 for subjects switching from SU to sitagliptin=8 weeks

Figure 1 Study Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subjects with T2DM with inadequate glycemic control on metformin and sitagliptin, who initiate and titrate insulin glargine (LANTUS®), to assess the effect of continuing sitagliptin relative to withdrawing sitagliptin on:

1) **Objective:** HbA_{1c} (A1C) after 30 weeks.

   Hypothesis A: After 30 weeks, continuing sitagliptin is non-inferior relative to withdrawing sitagliptin on the change from baseline in A1C.

   Hypothesis B: After 30 weeks, continuing sitagliptin results in a greater reduction of A1C relative to withdrawing sitagliptin.

2) **Objective:** the event rate of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) over 30 weeks.

   Hypothesis: Over 30 weeks, continuing sitagliptin results in a lower event rate of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) relative to withdrawing sitagliptin.

3) **Objective:** general safety and tolerability over 30 weeks.

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with T2DM with inadequate glycemic control on metformin and sitagliptin, who initiate and titrate insulin glargine (LANTUS®), to assess the effect of continuing sitagliptin relative to withdrawing sitagliptin on:

1) **Objective:** the incidence of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) over 30 weeks.

   Hypothesis: Over 30 weeks, continuing sitagliptin results in a lower incidence of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L).

2) **Objective:** the event rate of documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) over 30 weeks.

   Hypothesis: Over 30 weeks, continuing sitagliptin results in a lower event rate of documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) relative to withdrawing sitagliptin.

3) **Objective:** the incidence of documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) over 30 weeks.

   Hypothesis: Over 30 weeks, continuing sitagliptin results in a lower incidence of documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) relative to withdrawing sitagliptin.

4) **Objective:** the incidence of documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) over 30 weeks.

   Hypothesis: Over 30 weeks, continuing sitagliptin results in a lower incidence of documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) relative to withdrawing sitagliptin.

5) **Objective:** the daily dose of insulin after 30 weeks.

   Hypothesis: Over 30 weeks, continuing sitagliptin results in a lower daily dose of insulin relative to withdrawing sitagliptin.

6) **Objective:** the event rate of documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) over 30 weeks.

7) **Objective:** the event rate of documented hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) over 30 weeks.

8) **Objective:** the incidence of documented hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) over 30 weeks.

9) **Objective:** the proportion of subjects with A1C <7.0% [<53 mmol/mol] after 30 weeks.

10) **Objective:** the proportion of subjects with A1C <7.0% [<53 mmol/mol] after 30 weeks without any event of documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L).

11) **Objective:** fasting plasma glucose (FPG) after 30 weeks.

3.3 Exploratory Objectives

Objective: To evaluate the utility of continuous glucose monitoring (CGM) for comparing indices of blood glucose variability and hypoglycemia in subjects with T2DM on different treatment regimens.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to approved labeling for background information on sitagliptin, metformin, and insulin glargine (LANTUS®). In addition, refer to the Investigator Brochure (IB) for additional information on sitagliptin, including the Reference Safety Information (RSI).

4.1.1 Pharmaceutical and Therapeutic Background

Sitagliptin, a highly selective dipeptidyl peptidase-4 (DPP-4) inhibitor, improves fasting and postprandial glycemic control and measures of β-cell function in patients with T2DM. The effects of sitagliptin are mediated primarily through a glucose-dependent increase in insulin secretion and decrease in glucagon secretion. Sitagliptin is effective as monotherapy, as initial combination therapy with metformin, and as add-on therapy to other oral AHA agents.

A step-wise intensification of therapy as glycemic control either worsens or is not achieved is adopted for most patients with T2DM as it is a progressive disease [1]. The American Diabetes Association's (ADA) position statement on pharmacological therapy for T2DM recommends initiation of insulin (basal insulin alone as the most convenient regimen) as the second or third agent for patients who are unable to achieve their individualized A1C target after ~3 months of monotherapy or dual therapy [2]. In this paradigm of step-wise escalation of therapy, the recommendation is for insulin to be added to ongoing therapy with oral agents; however, combined therapy with oral agents and insulin has not been accepted as desirable by all experts [3]. Despite the advantages of continuing oral therapy when insulin is initiated, practitioners may choose to discontinue one or more of the oral agents the patient is on when insulin therapy is initiated.

The main disadvantages of this treatment paradigm are hypoglycemia and weight gain associated with insulin. Despite the fact that insulin is the most efficacious AHA agent available, and that large trials have shown that it is feasible to achieve an A1C target of ≤7.0% using insulin [4, 5, 6, 7], many patients on insulin fail to achieve glycemic goals [8]. This is likely related to the incidence of hypoglycemia and weight gain; a positive correlation has been described between the dose of insulin used and weight gain [9] and hypoglycemia [10].

Insulin therapy is typically initiated with basal insulin [2]. Basal insulin is most effective at directly controlling fasting plasma glucose; while a lower fasting glucose will result in lower post-meal glucose levels, an agent that provides postprandial glucose control such as sitagliptin will be likely to act in concert with basal insulin and improve post-meal glucose levels and overall glycemic control. It is also anticipated, as observed in two recent studies, MK-0431 P260 and the Sit2Mix trial [12], that the continued use of sitagliptin with basal insulin or premixed insulin will reduce the incidence of hypoglycemia, regardless of the glycemic control achieved and the dose of insulin required to achieve that degree of glycemic control.

In MK-0431 P260, it was demonstrated that the addition of sitagliptin in subjects who were intensely titrating insulin glargine (LANTUS®) based on a fasting glucose-based regimen not only resulted in a lower dose of insulin after 24 weeks, but also resulted in a lower incidence of hypoglycemia in the face of improved glycemic control (lower A1C and FPG) compared to the addition of placebo.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Based on the Clinical Practice Guidelines from the ADA, initiation of basal insulin is recommended for patients who have inadequate glycemic control on metformin ± DPP-4 inhibitors [2]. In particular, basal insulin (such as insulin glargine [LANTUS®]) is a common next step when patients are not at glycemic goal on metformin and a DPP-4 inhibitor such as sitagliptin; such an approach is consistent with the ADA Guidelines. In previous studies, including MK-0431 P260 referenced above, sitagliptin has been added to the treatment regimens of subjects on chronic insulin therapy; however, there are limited data on the use of sitagliptin at the time insulin therapy is initiated, and the utility of continuing sitagliptin when insulin therapy is initiated has not been clearly established. The Sit2Mix trial [12], a randomized 24-week trial, assessed the role of continuing sitagliptin in subjects with inadequate glycemic control (A1C 7.0%-10.0%) on metformin (at least 1000 mg/day) and sitagliptin (100 mg/day) with or without other oral AHA agents, when initiating premixed insulin. Subjects who discontinued sitagliptin when initiating twice-daily premixed insulin had inferior glycemic efficacy with a higher rate of hypoglycemia: after 24 weeks, the group that continued metformin and biphasic insulin aspart ± other AHAs but discontinued sitagliptin had a reduced glycemic response (compared to the group that discontinued sitagliptin, the group that continued sitagliptin had a better glycemic response with a between–group difference of -0.24% in A1C change from baseline [p=0.01]), a 40% lower odds of achieving the A1C goal of <7.0% (p=0.022), and a 48% lower odds of achieving the A1C goal of <7.0% without hypoglycemia (p=0.002) compared to the group that continued

sitagliptin along with metformin and biphasic insulin aspart ± other AHAs. However, the Sit2Mix was not a double-blinded trial. More recently, in a report from China, patients newly diagnosed with T2DM were assigned to receive continuous subcutaneous infusion of insulin aspart for 2 weeks, with or without sitagliptin, during which time the dose of insulin (basal and bolus) was also adjusted based on glycemic responses. At the end of the study period, patients in the sitagliptin group achieved lower glycated albumin levels, with a lower dose of insulin (in particular, the change from baseline in the dose of prandial insulin was lower in the sitagliptin group [−2.40 ± 3.65units/day compared to the control group 2.87 ± 5.81 units/day, p<0.01]), and with less time spent in hypoglycemia (<3.9 mmol/L/70 mg/dL) [13].

The present trial will assess the effect of continuing sitagliptin versus discontinuing sitagliptin (via randomized withdrawal of sitagliptin) when insulin is initiated and titrated in subjects with T2DM. Therefore, subjects with T2DM and inadequate glycemic control (i.e., A1C ≥7.5% to ≤11.0%) on pharmacotherapy with metformin (at near or maximally effective doses [≥1500 mg/d]) and sitagliptin will be randomized into the trial. To allow a broader subject population to participate, patients on other DPP-4 inhibitors in combination with metformin, or on metformin with a DPP-4 inhibitor and a sulfonylurea, or on metformin and a sulfonylurea can participate. Such subjects not currently on the dual combination of metformin and sitagliptin (as single entities) at Screening will be switched to this dual combination during the run-in period, and be eligible to continue in the study if they have inadequate glycemic control (A1C ≥7.5% and ≤11%) on this combination (please refer to Table 1 for details on how the various groups of subjects will be managed from Visit 1 through Visit 4).

Since sitagliptin is not approved in pediatric patients, the current study will only recruit patients 18 years of age and older.

4.2.2 Rationale for Dose Selection/Regimen

The dose of sitagliptin to be used (100 mg/day) is based upon the registered dose of sitagliptin for patients without moderate to severe renal insufficiency.

Please see Section 4.2.2.2 for the starting dose of insulin glargine (LANTUS®) to be used in this trial.

The duration of the double-blind treatment period (30 weeks) has been selected for the present study to allow sufficient time for patients to achieve optimal titration of their insulin dose.

4.2.2.1 Rationale for the Use of Placebo

Since sitagliptin is to be withdrawn in a random and double-blinded fashion, a matching sitagliptin placebo is required to maintain the blind in subjects who are assigned to the sitagliptin withdrawal arm.

4.2.2.2 Starting Dose for This Trial

Sitagliptin will be initiated at a dose of 100 mg/day and no changes will be made to the dose. Insulin glargine (LANTUS®) will be initiated at a dose of 10 units/day to be injected subcutaneously once daily in the evening [11, 14].

4.2.2.3 Maximum Dose/Exposure for This Trial

The dose of insulin glargine (LANTUS®) will be titrated based on the treat-to-target algorithm presented in Section 5.2.1.2. The dose of sitagliptin will not be modified during the trial.

4.2.3 Rationale for Endpoints

4.2.3.1 Key Efficacy Endpoints

1) Hemoglobin A_{1c} (A1C): A1C is an integrated measure of glycemic control over the previous ~3 months. Assessment of glycemic control through the calculation of placebo-subtracted change from baseline in A1C is standard in trials in subjects with T2DM.

2) Hypoglycemia: A primary objective of the study is to assess the effect of randomized withdrawal of sitagliptin on the event rate of hypoglycemia. While typically assessed as a safety endpoint, hypoglycemia is being evaluated as an efficacy endpoint in this trial, as the "efficacy" being sought is a lower event rate of hypoglycemia.

Incidence of hypoglycemia (defined as number of subjects with ≥1 event divided by number of subjects) is typically calculated for assessment of hypoglycemia. However, the true burden of hypoglycemia is not assessed with this endpoint, as subjects with multiple episodes are given the same weightage, in the calculation of incidence, as those with a single episode. Event rate of hypoglycemia (defined as the total number of events divided by total follow-up time) provides a more clinically relevant assessment of hypoglycemic burden to subjects. Therefore, this study will assess both event rates and incidence of hypoglycemia as endpoints.

The workgroup of the ADA and the Endocrine Society [15] has defined documented symptomatic hypoglycemia as an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L).

The workgroup has defined asymptomatic hypoglycemia as an event which is not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L).

In this study, the event rate and incidence of hypoglycemia accompanied by a measured (e.g., by fingerstick) glucose concentration of ≤70 mg/dL (≤3.9 mmol/L) will be assessed as key efficacy endpoints.

More recently, Muchmore et al [16] have suggested that when using self-monitored blood glucose values to define hypoglycemia in clinical trials, a cut-off of <56 mg/dL may be relevant to accommodate the currently allowed measurement error of ±15 mg/dL for plasma glucose values <75 mg/dL in home glucose monitoring meters. For this reason, the event rate and incidence of hypoglycemia accompanied by a measured glucose concentration of <56 mg/dL (≤3.1 mmol/L) will be assessed as another set of key efficacy endpoints.

3) Insulin dose: Since the continuation of sitagliptin may result in better glycemic efficacy by controlling fasting and postprandial glucose, it is possible that a lower dose of insulin is required in subjects who continue sitagliptin. Therefore, determination of the placebo-adjusted change from baseline in insulin dose will allow the assessment of the effect that randomized withdrawal of sitagliptin has on the dose of insulin achieved through intense titration of insulin glargine (LANTUS®).

4) Fasting plasma glucose (FPG): Placebo-adjusted changes from baseline in FPG will allow the assessment of the effect that randomized withdrawal of sitagliptin has on measures of fasting glycemic control. In addition, assessment of FPG may indicate the extent to which insulin glargine (LANTUS®) was titrated, based on a fasting-glucose based regimen.

4.2.3.2 Key Safety Endpoints

Assessment of overall safety: As is standard practice, the overall safety and tolerability of continuing sitagliptin when insulin is initiated will be assessed, including the occurrence of adverse events of hypoglycemia.

4.2.3.3 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation. However, in this study since subjects in both treatment arms will be getting standard-care treatment (intensively titrating insulin to achieve a glycemic target of fasting glucose of 72-100 mg/dL), it is anticipated that all participants will benefit from improved glycemic control.

The risk of hypoglycemia from the titration of insulin will be balanced by the benefits of improvements in glycemic control.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with T2DM ≥18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

At Visit 1/Screening

1. Have T2DM (based on ADA guidelines [17]) and be ≥18 years of age on the day of signing informed consent.
2. Be on one of the following treatment regimens:
    a. stable dose of sitagliptin (100 mg/day) and metformin IR or XR (≥1500 mg/day) either co-administered or as a FDC for ≥12 weeks with A1C between 7.5% and 11.0% (≥58 mmol/mol and ≤ 97 mmol/mol), inclusive.

    OR

    b. stable dose of metformin IR or XR (≥1500 mg/day) and another DPP-4 inhibitor (at maximum labeled dose, see Table 1), other than sitagliptin, either co-administered or as a FDC, for ≥12 weeks with A1C between 7.5% and 11.0% (≥58 mmol/mol and ≤ 97 mmol/mol), inclusive.

    OR

    c. stable dose of sitagliptin (100 mg/day) and metformin IR or XR (≥1500 mg/day) either co-administered or as a FDC, **and** a sulfonylurea for ≥12 weeks **OR** stable dose of metformin IR or XR (≥1500 mg/day) and a sulfonylurea administered as a FDC and sitagliptin (100 mg/day) with A1C between 7.0% and 10.0% (≥53 mmol/mol and ≤86 mmol/mol), inclusive.

    OR

d. stable dose of metformin IR or XR (≥1500 mg/day) and another DPP-4 inhibitor (at maximum labeled dose, see Table 1), other than sitagliptin, either co-administered or as a FDC, **and** a sulfonylurea for ≥12 weeks **OR** stable dose of metformin IR or XR (≥1500 mg/day) and a sulfonylurea administered as a FDC and another DPP-4 inhibitor other than sitagliptin with A1C between 7.0% and 10.0% (≥53 mmol/mol and ≤86 mmol/mol), inclusive.

   OR

e. stable dose of metformin IR or XR (≥1500 mg/day) and a sulfonylurea either co-administered or as a FDC for ≥12 weeks with A1C between 7.5% and 11.0% (≥58 mmol/mol and ≤ 97 mmol/mol), inclusive.

3. Understand the study procedures, alternative treatments available, and risks involved with the study; be willing and able to comply with study procedures and scheduled visits, treatment plan, laboratory tests, and other study procedures; is not planning to relocate during the study; and has personally signed and dated the ICF indicating that he/she has been informed of all pertinent aspects of the trial and voluntarily agrees to participate.

   Note: The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

4. Meet one of the following categories:

   a. The subject is a male.

   b. The subject is a female who is not of reproductive potential, defined as a female who either:

      i. is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age);

      ii. has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening;

      iii. has a congenital or acquired condition that prevents childbearing.

   c. The subject is a female who is of reproductive potential and agrees to avoid becoming pregnant while receiving study drug and for 14 days after the last dose of study drug by complying with one of the following:

      i. practice abstinence[†] from heterosexual activity

         OR

      ii. use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are[‡]:

         - intrauterine device (IUD)
         - vasectomy of a female subject's male partner
         - contraceptive rod implanted into the skin

- hormonal contraception including vaginal rings
- condoms
- diaphragm with spermicide
- contraceptive sponge

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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

At Visit 3

5. A1C of 7.5% to 11.0% (≥58 mmol/mol and ≤ 97 mmol/mol).

   Note: Subjects already on dual combination metformin (IR or XR) and sitagliptin (as single entities or FDC) at protocol-specified doses at Visit 1/Screening, should use the Screening Visit A1C value to assess eligibility and **do not need a repeat A1C**, if the Screening A1C value was measured within **2 weeks** of the combined Visit 2/3/4 [Randomization/Day 1]).

5.1.3 Subject Exclusion Criteria

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

At Visit 1/Screening

Glucose Metabolism and Therapy Criteria

1. Has been treated with any AHA other than protocol-specified agents (i.e., other than metformin, DPP-4 inhibitor, or sulfonylurea agent) within the prior 12 weeks.
2. Has a history of 2 or more episodes of hypoglycemia resulting in seizure, coma, or loss of consciousness, OR subject has had recurrent (≥3 times per week) episodes of hypoglycemia over the past 8 weeks.
3. Has a history of type 1 diabetes mellitus (T1DM) or ketoacidosis, or has a history of latent autoimmune diabetes of adults (LADA), or subject is assessed by the investigator as possibly having T1DM or LADA confirmed with a C-peptide <0.7 ng/mL (<0.23 nmol/L), or has a history of other specific types of diabetes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, or post-organ transplant).

   Note: Only a subject assessed by the investigator as possibly having T1DM or LADA should have C-peptide measured at Visit 1/Screening Visit.
4. Is assessed by the investigator to be not appropriate for, or does not agree to target, a fasting glucose of 72-100 mg/dL (4.0-5.6 mmol/L).

Requirement for Specific Treatments

5. Has a history of intolerance or hypersensitivity to sitagliptin, or insulin, or any contraindication to sitagliptin, or insulin, based upon the label of the country of the investigational site.
6. Has undergone a surgical procedure within 12 weeks and is not fully recovered prior to signing informed consent or has planned major surgery during the study.

   Note: A subject who has undergone minor surgery within the prior 4 weeks and is fully recovered or a subject who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia.
7. Is currently participating, or has participated, in a study in which the subject 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 subject who has participated in a non-interventional study may be enrolled.
8. Is on a weight loss program and not in the weight-stable phase (including diet and or medications for weight loss), or has undergone bariatric surgery within 12 months prior to signing the informed consent.
9. Is currently on or likely to require treatment with a prohibited medication (see Section 5.5.2 for a list of excluded medications). Example: is on, or likely to require treatment with more than 14 consecutive days or repeated courses of pharmacologic doses of corticosteroids.

   Note: Oral corticosteroids used for physiologic replacement therapy (i.e., in subjects with adrenal insufficiency) and inhaled, nasal, and topical corticosteroids are allowed.

Concomitant Disease of Organs and Systems

10. 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), or had new or worsening signs or symptoms of coronary heart disease or 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.
11. Has human immunodeficiency virus (HIV) infection
    a. with AIDS-related complications, or
    b. has not been on a stable antiretroviral regimen for >6 months, or
    c. has progressive disease, or

d. is using agents associated with glucose intolerance such as nucleoside reverse transcriptase inhibitors (NRTIs) such as azidothymidine (AZT), didanosine (ddI) and stavudine (d4T).

12. Has a history of malignancy ≤5 years prior to signing informed consent (i.e., the diagnosis occurred, or any evidence of residual or recurrent disease occurred, within the past 5 years), except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.

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

Exclusion Criteria Based on Lab Abnormalities

13. Has an exclusionary laboratory value as listed in Table 2 below.

Table 2 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 Alanine Aminotransferase (ALT)		>2-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	<11.0 g/dL
	Female	<10.0 g/dL
Total Triglycerides (TG)[4]		>600 mg/dL (6.8 mmol/L)

[1] Subjects with an exclusionary laboratory value may have one repeat determination performed if the investigator considers the Visit 1/Screening result to be inconsistent with prior determinations. Only the lab test not meeting entry criterion should be repeated (not the entire panel). The last laboratory draw/result should be used for inclusion.
[2] Calculated by the central laboratory using the 4-variable MDRD equation.
[3] Subject excluded due to TSH criterion may be re-screened after being on a stable thyroid replacement regimen for at least 6 weeks.
[4] Subjects with elevated TG levels, who would qualify for a combined Visit 2/3/4, may be re-screened after being on a stable lipid-lowering regimen for at least 4 weeks. All other subjects (i.e., subjects who require Visits 2 and 3, prior to randomization at Visit 4) with elevated TG levels, may have lipid-lowering medication initiated or adjusted and continue in the trial if a repeat measurement (at Visit 3/Week -1) no longer meets the exclusion criterion. All subjects must be on a stable dose of a lipid-lowering medication for at least 4 weeks prior to Visit 4/Randomization (Day 1).

Other Criteria

14. Is pregnant or breast-feeding, has a positive urine pregnancy test, or is expecting to conceive or donate eggs during the study, including 14 days following the last dose of study drug.

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

16. Has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance that
    a. makes participation not in the subject's best interest
    b. might interfere with the subject's participation for the full duration of the study
    c. might confound the results of the study.
17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

At Visit 4/Day 1/Randomization

18. Has a positive urine pregnancy test.

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

19. Has a clinically significant ECG finding that requires further diagnostic evaluation or intervention (e.g., new, clinically significant arrhythmia or a conduction disturbance) or which exposes the subject to risk by enrolling in the study.
20. 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 subject to risk by enrolling in the study.

    Note: If a subject requires initiation of a new medication at Visit 4/Day 1, the subject should be rescheduled for a Visit 4/Day 1 to occur 1 to 2 weeks later.

21. Has a site fasting fingerstick glucose of <130 mg/dL (7.2 mmol/L) or >270 mg/dL (15.0 mmol/L).

    Note: If the subject meets this exclusion criterion AND the investigator believes that the value is not consistent with the subject's current Self-Monitoring Blood Glucose (SMBG) values and the Visit 1 or Visit 3/Week -1 FPG value (as applicable), the subject should not be excluded at this time. This value can be repeated and the subject should be rescheduled for Visit 4/Day 1 within 7 days. If the subject meets this FFSG exclusion criterion at the rescheduled Visit 4/Day 1, the subject MUST be excluded.

5.2 Trial Treatment(s)

Treatments to be used in this trial are outlined below in Table 3.

Table 3 Trial Treatment

Treatment	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Sitagliptin	100 mg	QD	Oral	Visit 1 (or Visit 2) through Visit 9	Experimental from V4
Sitagliptin-matching Placebo	Not applicable	QD	Oral	Visit 4 through Visit 9	Placebo-comparator
Metformin[a]	At least 1500 mg/day	As applicable, based upon the local label or clinical practice guidelines	Oral	Visit 1 through Visit 9	Background therapy
Metformin XR[b]	At least 1500 mg/day	QD	Oral	Visit 1 through Visit 9	Background therapy
Insulin Glargine (LANTUS®)	Starting dose: 10 units. To be titrated based on treat-to-target regimen	QD	SC	Visit 4 through Visit 9	Background therapy

a. For subjects entering the study on immediate-release metformin + sitagliptin or a FDC.
b. For subjects entering the study on extended-release metformin + sitagliptin or a FDC.

The first dose of trial treatment will be administered at the trial site at Visit 4 (i.e., the beginning of the double-blind treatment period). Subsequent dosing will be performed once daily by the subject (i.e., unsupervised at his/her home) at approximately the same time each day.

Run-in Period

Subjects will enter the Screening period (at Visit 1) on metformin and sitagliptin (with or without a sulfonylurea), metformin and another DPP-4 inhibitor (with or without a sulfonylurea), or metformin and a sulfonylurea. If on metformin, sitagliptin and a sulfonylurea, eligible subjects will discontinue the sulfonylurea at Visit 2; if on metformin, another DPP-4 inhibitor and a sulfonylurea, eligible subjects will discontinue the sulfonylurea and switch their other DPP-4i to sitagliptin 100 mg at Visit 2; if on metformin and a sulfonylurea, eligible subjects will discontinue the sulfonylurea and switch to sitagliptin 100 mg at Visit 2.

Double-Blind Treatment Period

On Day 1/Randomization (combined Visit 2/3/4 OR Visit 4), eligible subjects will be randomized to either continue sitagliptin, or switch to sitagliptin-matching placebo (i.e., randomized, double-blind withdrawal of sitagliptin) for the remainder of the trial and initiate and titrate insulin glargine (LANTUS®) therapy (starting dose of 10 Units in all patients, refer to Section 5.2.1.2).

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Modification of Sitagliptin/Matching Placebo to Sitagliptin

The dose of sitagliptin or matching placebo cannot be modified throughout the 30-week double-blind treatment period.

If a subject is suspected of having pancreatitis, study medications should be interrupted; study medications may be re-initiated if pancreatitis is not confirmed.

5.2.1.3 Dose Modification (Titration) of Insulin Glargine (LANTUS®)

Beginning at Visit 4/Randomization (Day 1), Investigators will instruct subjects to initiate 10 units of insulin glargine (LANTUS®) and to titrate their insulin glargine (LANTUS®) dose to treat-to-target levels as described below in Table 4. The target is a FFSG (before breakfast) or FPG (before breakfast) of 72-100 mg/dL (4.0-5.6 mmol/L).

Table 4 Insulin Glargine (LANTUS®) Titration Based on Fasting Glucose

Fasting Glucose Measurements (Before Breakfast	Change in Insulin Glargine (LANTUS®) Dose
>100 mg/dL (5.6 mmol/L)*	Increase dose by 2U
>140 mg/dL (7.8 mmol/L)**	Increase dose by 4U
≤70 mg/dL (3.9 mmol/L) at any time	Reduce insulin dose by 4U (or as instructed by study physician)
Goal is fasting glucose (before breakfast) of 72-100 mg/dL (4.0-5.6 mmol/L) * If the fasting glucose measurements on 3 consecutive days are all >100 mg/dL the insulin dose will be increased by 2 units. ** If the fasting glucose measurements on 3 consecutive days are all >140 mg/dL the insulin dose will be increased by 4 units.	

Adherence of subjects to the titration algorithm will be monitored at Patient Telephone Contacts (PTCs) and scheduled visits. For subjects who do not follow the insulin titration algorithm outlined above, more frequent PTCs will be necessary to make sure that the insulin titration algorithm is closely followed by the subject.

For subjects who experience hypoglycemia with FPG or fingerstick glucose values ≤70 mg/dL (3.9 mmol/L), the insulin glargine (LANTUS®) dose should be reduced as described in the table, and, if necessary, held.

Refer to Sections 7.1.1.8.2 and 7.1.1.8.3 for details regarding appropriate subject documentation of fingerstick glucose values and hypoglycemia events.

5.2.1.4 Dose Modification of Metformin

The dose of metformin (≥1500 mg/day) should remain stable throughout the 30-week double-blind treatment period.

If a subject undergoes an imaging study requiring the use of radiocontrast dye (e.g., an intravenous pyelogram or computerized tomography study with contrast), metformin should be interrupted and reinstituted only after renal function has been evaluated and found not to have been reduced by the dye study.

5.2.2 Timing of Dose Administration

Subjects will take double-blind study medication (sitagliptin or sitagliptin-matching placebo) QD, at approximately the same time every day.

Subjects will take either open-label metformin or metformin XR, as directed by the study doctor, but should remain on a stable regimen (including dose frequency) throughout the trial.

Subjects will be trained to administer insulin glargine (LANTUS®) once a day, at the same time every evening. As noted in Section 5.2.1.2, dose titration will be determined by the treat-to-target algorithm.

Subjects will be instructed not to take open-label metformin and double-blind study medication the morning of clinic visits. On clinic visit days, subjects will take open-label metformin and blinded study medication after all study procedures are completed.

If a subject misses a dose of open-label metformin or blinded study medication during the trial, he/she should be instructed to take it as soon as they remember, unless it is time for the next dose. Subjects should be instructed not to "make up" for the missed dose by taking two doses at the same time. Subjects who miss the dose of insulin glargine (LANTUS®) should call the site as soon as possible.

5.2.3 Trial Blinding/Masking

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

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

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to either sitagliptin 100 mg or sitagliptin-matching placebo.

5.4 Stratification

Treatment allocation/randomization will be stratified according to the following factor:

AHA treatment at screening:

- Metformin + sitagliptin/another DPP-4 inhibitor (Met + DPP-4i)
- Metformin + sitagliptin/another DPP-4 inhibitor + sulfonylurea (Met + DPP-4i + SU)
- Metformin + sulfonylurea (Met + SU).

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Any medications taken by the subject within 15 weeks of Visit 1/Screening, including AHA medications, should be recorded on the appropriate electronic case report form (eCRF). The site may rely on subject report for this information. Concomitant medications taken during the trial must also be recorded.

Subjects should be questioned about their use of concomitant medications at the time points indicated in the Trial Flow Chart (Section 6.0). Subjects should be instructed to contact the study investigator before initiating any prescription or non-prescription medications during study participation. If medical necessity requires initiation of a medication prior to discussion with the study investigator, the subject should communicate with the study investigator as soon as possible.

5.5.1 Allowed Medications

Lipid Medications

Concurrent lipid lowering medications are permitted. Subjects with elevated TG levels, who would qualify for a combined Visit 2/3/4, may be re-screened after being on a stable lipid-lowering regimen for at least 4 weeks. All other subjects (i.e., subjects who require Visits 2 and 3, prior to randomization at Visit 4) with elevated TG levels, may have lipid-lowering medication initiated or adjusted and continue in the trial if a repeat measurement (at Visit 3/Week -1) no longer meets the exclusion criterion. All subjects must be on a stable dose of a lipid-lowering medication for at least 4 weeks prior to Visit 4/Randomization (Day 1), refer to Section 5.1.3, Table 2.

Blood Pressure Medications

Concurrent blood pressure lowering medications are permitted. Subjects with elevated systolic and/or diastolic blood pressure levels, who would qualify for a combined Visit 2/3/4, may be re-screened after being on a stable blood pressure-lowering regimen for at least 4 weeks. All other subjects (i.e., subjects who require Visits 2 and 3, prior to randomization at Visit 4) with elevated BP levels, may have blood pressure medication initiated or adjusted and continue in the trial. Subjects must be on a stable regimen for at least 4 weeks prior to Visit 4/Randomization (Day 1).

It is preferable that doses of these medications remain stable during the double-blind treatment period.

Thyroid Hormone Replacement Therapy

Subjects must be on a stable dose of thyroid replacement medication (e.g., thyroxine) for at least 6 weeks prior to Visit 1/Screening Visit. Subjects who meet the TSH exclusion criterion specified in Table 2 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 subjects 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. Subjects who do not discontinue the use of such supplements prior to Visit 4 should be instructed not to change the use or dose of the supplement for the duration of the study. Subjects should be instructed not to initiate new supplements for the duration of the study.

5.5.2 Excluded Medication(s)/Treatment(s)

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication specifically prohibited during the trial, discontinuation from trial therapy will be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the subject cannot continue on trial therapy if a prohibited medication is required.

NOTE: At the time points indicated in the Trial Flow Chart (Section 6.0), investigational sites should review the use of any prohibited medications, including AHAs with subjects who are on double-blind study medication. At these time points, subjects should be instructed regarding the importance of not taking AHAs other than metformin, insulin glargine (LANTUS®), and blinded study medication (sitagliptin/placebo) during study participation.

Other AHA Medications

Except for sitagliptin, metformin, and insulin glargine (LANTUS®) that are part of the study protocol, no other AHA medication (such as DPP-4 inhibitors [other than sitagliptin], GLP-1 analogues, sulfonylureas, meglitinides, α-glucosidase inhibitors, PPAR-γ agonists, bromocriptine, or colesevelam) may be taken during the study. Rapid- and intermediate-acting insulin and other basal insulins should not 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 and oral corticosteroids for replacement therapy are permitted.

Anti-Thyroid Medications

Medications to treat hyperthyroidism are prohibited.

5.5.3 Excluded Medication(s)/Treatment(s) Applicable to Only CGM Subjects:

Subjects should not use acetaminophen and/or medications containing acetaminophen for at least 24 hours prior to sensor insertion and while the sensor is being used.

5.6 Rescue Medications & Supportive Care

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at Visits 2, 3, and 4 or the combined Visit 2/3/4 (as applicable); follow-up at other visits may be done by other appropriate site personnel evaluating the subject.

The subject will receive counseling on diet consistent with the local guidelines of the country of the investigational site. At each subsequent visit, the subject will be asked about their diet and exercise, and counseling should be provided, as appropriate. Detailed dietary information will not be captured.

5.7.2 Alcohol, Caffeine and Tobacco

- Subjects will be counseled to limit alcohol use to moderate amounts (i.e., ≤2 drinks per day and no more than 14 drinks per week).
- Ingestion of caffeine will be prohibited for at least 30 minutes prior to scheduled ECGs and blood pressure determinations.
- Ingestion of nicotine-containing products will be prohibited for at least 30 minutes prior to the scheduled ECGs and blood pressure determinations.

5.7.3 Activity

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

  Note: See Section 5.8.1 for additional details regarding subjects who withdraw consent and subjects who do not withdraw consent but discontinue study drug.

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

1. Abnormal liver function tests meeting criteria specified below (see Section 12.4 for additional details on management and discontinuation of blinded study drug for subjects with elevated liver enzymes).
   - ALT or AST ≥3X ULN with total bilirubin (TBL) ≥2X ULN and alkaline phosphatase (ALP) <2X ULN and without an established etiology; or
   - ALT or AST ≥8X ULN or ≥3X ULN with symptoms consistent with liver injury and without an established etiology; or
   - ALT or AST ≥5X ULN for 2 weeks; or
   - ALT or AST ≥3X ULN and subject is unwilling or unable to undergo repeat ALT and AST testing at the frequency defined in Section 12.4.
2. Reduction of renal function:
   - eGFR persistently <50 mL/min/1.73m^2 (MDRD formula).

     Note: A persistent eGFR value is defined as a repeat measurement, performed within 2 weeks after notification from the central laboratory, that remains <50 mL/min/1.73m^2, despite correction of potential causative factors (e.g., correction of volume depletion, discontinuation of nonsteroidal anti-inflammatory drugs [NSAIDs]).

3. Requirement for one of the prohibited medications listed in Section 5.5.2.
4. Pregnancy.

   Note: A positive urine pregnancy test requires immediate interruption of blinded study drug, metformin, and insulin glargine (LANTUS®) until serum β-hCG can be performed and found to be negative. Subject must be permanently discontinued from blinded study drug, metformin, and insulin glargine (LANTUS®) and pregnancy should be reported and followed per Section 7.2.2 if pregnancy is confirmed by a positive serum pregnancy test.
5. Any medical condition or personal circumstance which, in the opinion of the investigator, exposes the subject to risk by continuing in the trial or does not allow the subject to adhere to the requirements of the protocol.
6. The investigator or subject becomes unblinded to the subject's treatment assignment.

The Sponsor should be notified as soon as possible when a subject is discontinued from blinded study drug or blinded study drug is interrupted because of an AE or a laboratory safety test abnormality.

A subject may discontinue blinded study drug for any of the reasons listed above but continue to participate in the trial, as long as the subject does not withdraw consent. Follow-up procedures for subjects who discontinue blinded study drug are described in Section 5.8.1.1.

5.8.1 Follow-up for Subjects Who Discontinue Blinded Study Drug

5.8.1.1 Withdrawal of Consent

If a subject indicates his or her intention to stop active participation in the trial (i.e., chooses to no longer attend visits at the investigational site, take blinded study drug, and have other study-related procedures conducted at the investigational site) and withdraws consent, the subject should be encouraged to complete procedures for the Discontinuation Visit (when they discontinue blinded study therapy and withdraw consent) followed by a post-treatment telephone call 14 days after the last dose of blinded study drug. The purpose of the 14-day post-treatment telephone call is to collect information about the subject's health status (e.g., evaluate if the subject experienced any SAEs).

The sponsor may retain and continue to use any data collected before the subject's withdrawal of consent.

5.8.1.2 Discontinuation from Blinded Study Therapy

A subject who discontinues treatment with blinded study drug for reasons other than withdrawn consent or a subject for whom the investigator recommends discontinuation of study medication should complete procedures for the Discontinuation Visit followed by a post-treatment telephone call 14 days after the last dose of blinded study drug. The subject should then be requested to return to the study site for all scheduled visits for safety and efficacy evaluations. If the subject is unwilling to return for the scheduled study visits, alternative efforts should be made to collect safety and efficacy information; this may include participating in telephone contacts according to the study schedule until the end of the trial (Week 30). The purpose of these telephone contacts is to collect information about the subject's health status (e.g., evaluate if the subject experienced any SAEs).

A subject who continues to participate in the trial off of study medication by providing follow-up information (whether attending scheduled visits at the investigational site or through follow-up telephone contact visits) can receive medical and diabetes management by his/her managing physician or investigator, as appropriate. This subject may initiate any other therapy as needed (previously prohibited medications will not apply to him/her). Procurement of other AHAs is the responsibility of the subject.

If the trial site loses contact with the subject, the site should make at least three attempts for a telephone contact. If the three attempts of telephone contact are unsuccessful, the site should make at least one attempt to reach the subject via certified letter. All attempts to contact a subject and information received during contact attempts must be documented in the subject's medical record.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

5.11 Clinical Criteria for Early Trial Termination

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

6.0 TRIAL FLOW CHART

Trial Period:	Screening[a]	Pre-randomization[b]		Randomization	Double-Blind Treatment										Post-Treatment	
Visit Number/Title:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**PTC**	**Visit 5**	**PTC**	**Visit 6**	**PTC**	**Visit 7**	**PTC**	**Visit 8**	**PTC**	**Visit 9**	**D/C**	**Follow-up**
Scheduled Hour, Day, Week etc.:			Week -1	Week 0 (Day 1)	Weeks 1, 2, 4	Week 6	Weeks 8, 10	Week 12	Week 15	Week 18	Week 21	Week 24	Week 27	Week 30	At time of D/C[c]	14-Day Post Treatment TC
Scheduling Window Hours, Days etc.:			± 5 days	+7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days		+3 days
Administrative Procedures																
Informed Consent	X															
Informed Consent for Future Biomedical Research[d]	X															
Assignment of Screening Number	X															
Contact IVRS	X	X		X		X		X		X		X		X	X	
Inclusion/Exclusion Criteria	X	X	X	X												
Dispense Subject Identification Card	X															
Demographics and Medical History	X															
Review Prior/Concomitant Medication[e]	X	X	X	X		X		X		X		X		X	X	
Review use of any prohibited medications, including AHAs; counsel patients on importance of not taking other AHAs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assignment of Randomization Number				X												
Instruct subjects to switch current DPP-4i and/or discontinue or switch SU (as applicable)[f,g]		X														

Trial Period:	Screening[a]	Pre-randomization[b]		Randomization	Double-Blind Treatment										Post-Treatment	
Visit Number/Title:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**PTC**	**Visit 5**	**PTC**	**Visit 6**	**PTC**	**Visit 7**	**PTC**	**Visit 8**	**PTC**	**Visit 9**	**D/C**	**Follow-up**
Scheduled Hour, Day, Week etc.:			Week -1	Week 0 (Day 1)	Weeks 1, 2, 4	Week 6	Weeks 8, 10	Week 12	Week 15	Week 18	Week 21	Week 24	Week 27	Week 30	At time of D/C[c]	14-Day Post Treatment TC
Scheduling Window Hours, Days etc.:			± 5 days	+7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days		+3 days
Diet and Exercise Counseling/Monitoring[h]		X	X	X		X		X		X		X				
Dispense Hypoglycemia Assessment Log (HAL) and Instruct on Hypoglycemia Symptoms and Management		X		X[1]												
Dispense Blood Glucose Meter / Provide Self-Monitoring Blood Glucose (SMBG) Instruction		X		X[1]												
Study Medication																
Dispense Open-Label Study Drug		X														
Switch Subjects on Fixed Dose Combination Product to Single Entity Tablets				X												
Witness Blinded Dose of Study Drug in Clinic				X												
Dispense Double-Blind Study Drug				X		X		X		X		X				
Assess Compliance with Study Medication						X		X		X		X		X	X	
Clinical Procedures/Assessments																
Vital Signs Measured in Duplicate (Heart Rate, Blood Pressure[j])	X			X		X		X		X		X		X	X	

Trial Period:	Screening[a]	Pre-randomization[b]		Randomization	Double-Blind Treatment										Post-Treatment	
Visit Number/Title:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**PTC**	**Visit 5**	**PTC**	**Visit 6**	**PTC**	**Visit 7**	**PTC**	**Visit 8**	**PTC**	**Visit 9**	**D/C**	**Follow-up**
Scheduled Hour, Day, Week etc.:			Week -1	Week 0 (Day 1)	Weeks 1, 2, 4	Week 6	Weeks 8, 10	Week 12	Week 15	Week 18	Week 21	Week 24	Week 27	Week 30	At time of D/C[c]	14-Day Post Treatment TC
Scheduling Window Hours, Days etc.:			± 5 days	+7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days		+3 days
Full Physical Examination				X												
Brief Physical Examination[k]														X	X	
Height (Measured in Duplicate)	X															
Weight (Measured in Duplicate)	X			X		X		X		X		X		X	X	
Site A1C Fingerstick Measurement	X[l]															
12-Lead Electrocardiogram (Read Locally)				X												
Fasting Fingerstick Glucose in Clinic				X[m]												
Review of SMBG Measurements and HAL[n]			X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Telephone Contact (PTC) to Assess Insulin Titration					X		X		X		X		X			
Continuous Glucose Monitoring (CGM)[o]				X[p]				X[q]						X[p]		
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments																
Hematology Panel	X															
Chemistry Panel[r]	X			X[s]										X	X	
Fasting Plasma Glucose (FPG)	X		X	X		X		X		X		X		X	X	
Hemoglobin A_{1C} (A1C)	X		X	X[s]		X		X		X		X		X	X	

Trial Period:	Screening[a]	Pre-randomization[b]		Randomization	Double-Blind Treatment										Post-Treatment	
Visit Number/Title:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**PTC**	**Visit 5**	**PTC**	**Visit 6**	**PTC**	**Visit 7**	**PTC**	**Visit 8**	**PTC**	**Visit 9**	**D/C**	**Follow-up**
Scheduled Hour, Day, Week etc.:			Week -1	Week 0 (Day 1)	Weeks 1, 2, 4	Week 6	Weeks 8, 10	Week 12	Week 15	Week 18	Week 21	Week 24	Week 27	Week 30	At time of D/C[c]	14-Day Post Treatment TC
Scheduling Window Hours, Days etc.:			± 5 days	+7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days		+3 days
Fasting C-Peptide[t]	X															
Lipid Panel				X										X	X	
Thyroid Stimulating Hormone (TSH)	X[u]															
Fasting Triglycerides	X[v]															
Urine Pregnancy Test (as applicable)[w]	X			X		X		X		X		X		X	X	
Dipstick Urinalysis	X[x]															
Plasma and Serum for Future Biomedical Research[d]				X										X	X	
Blood (DNA) for Future Biomedical Research[c]				X												

a. Screening procedures may be repeated after consultation with the Sponsor.
b. The pre-randomization period (Visits 2 and 3) only applies to subjects on another DPP-4 inhibitor and/or a SU at Visit 1/Screening.
c. A subject who withdraws from the study prematurely should be encouraged to complete procedures for the Discontinuation Visit and allow to be followed by the investigator/qualified designee according to Section 5.8.1.
d. Informed consent for future biomedical research samples must be obtained to collect the DNA, plasma, and serum sample.
e. Subjects on double-blind treatment should be reminded **not to take any other AHA medications other than the trial treatments** (background metformin and insulin glargine [LANTUS®], and sitagliptin/placebo) during their participation in the study. They should be counseled that if another physician prescribes such a treatment (i.e., any AHA), the subject and/or the prescribing physician should immediately contact the investigational site prior to initiation of such therapy. If medical necessity requires initiation of a medication prior to discussion with the study investigator, the subject should communicate with the study investigator as soon as possible. Subjects who were washed off of another AHA should be reminded to remain off this agent while participating in the current trial, and to not re-start this agent post-study unless advised by their diabetes care-giver (whether the investigator or another physician).
f. Subjects who have switched from another DPP-4 inhibitor to sitagliptin and/or initiated sulfonylurea wash-off at Visit 2 should be on sitagliptin and/or have washed off the sulfonylurea for at least 4 weeks prior to Visit 4/Randomization; the interval between Visit 2 and Visit 3 should be at least 3 weeks.
g. Subjects who have switched from a sulfonylurea to sitagliptin at Visit 2 should be on sitagliptin for at least 8 weeks prior to Visit 4/Randomization; the interval between Visit 2 and Visit 3 should be at least 7 weeks.
h. The subject will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at Visits 2, 3, and 4 or the combined Visit 2/3/4 (as applicable); follow-up at other visits may be done by other appropriate site personnel evaluating the subject.
i. Activity applies to subjects attending the combined Visit 2/3/4 only.

Trial Period:	Screening[a]	Pre-randomization[b]		Randomization	Double-Blind Treatment										Post-Treatment	
Visit Number/Title:	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**PTC**	**Visit 5**	**PTC**	**Visit 6**	**PTC**	**Visit 7**	**PTC**	**Visit 8**	**PTC**	**Visit 9**	**D/C**	**Follow-up**
Scheduled Hour, Day, Week etc.:			Week -1	Week 0 (Day 1)	Weeks 1, 2, 4	Week 6	Weeks 8, 10	Week 12	Week 15	Week 18	Week 21	Week 24	Week 27	Week 30	At time of D/C[c]	14-Day Post Treatment TC
Scheduling Window Hours, Days etc.:			± 5 days	+7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days	± 1 day	± 7 days		+3 days

j. Subjects with elevated systolic and/or diastolic blood pressure levels, who would qualify for a combined Visit 2/3/4, may be re-screened after being on a stable blood pressure-lowering regimen for at least 4 weeks. All other subjects (i.e., subjects who require Visits 2 and 3, prior to randomization at Visit 4) with elevated BP levels, may have blood pressure medication initiated or adjusted and continue in the trial. Subjects must be on a stable regimen for at least 4 weeks prior to Visit 4/Randomization (Day 1).

k. Brief physical examination includes assessment of heart, lungs, abdomen, extremities and skin.

l. Site fingerstick A1C is not mandatory, but may be used, at the discretion of the investigator, for screening a subject. However, a fingerstick A1C cannot substitute for a central laboratory measured A1C to determine if a subject meets entry criteria.

m. FFSG values performed in the clinic will be used to assess subject eligibility prior to randomization.

n. SMBG measurements (FSG Log) and the HAL will be reviewed at Visit 3 and Visit 4 for subjects who require Visits 2, 3, and 4 as separate visits. Additionally, these logs will be reviewed at all clinic visits and telephone contacts after Visit 4/Randomization (Day 1) for all subjects and will be used to assess for events of hypoglycemia.

o. Continuous glucose monitoring (CGM) to be conducted in a subset of study subjects (n=~50-80). Subjects participating in the CGM sub-study should not use acetaminophen and/or medications containing acetaminophen for at least 24 hours prior to sensor insertion and while the sensor is being used.

p. CGM sensor and device should be placed ~1-2 weeks before the Randomization and Week 30 Visits, and removed with data downloaded at the Randomization and Week 30 visits, respectively.

q. CGM sensor and device should be placed at the Week 12 visit and removed with data downloaded at the clinic ~1-2 weeks later.

r. Measurements include liver function tests (ALT, AST, alkaline phosphatase, total bilirubin [indirect and direct bilirubin, if the total bilirubin is >ULN]) and calculation of eGFR (MDRD formula).

s. If a combined Visit 2/3/4 occurs within 2 weeks after Visit 1/Screening, it is not necessary to repeat A1C and chemistry panel tests at the combined visit. The Visit 1 results from these assessments may be used to satisfy entry criteria.

t. Fasting C-peptide test at Visit 1/Screening is only for a subject assessed by the investigator as possibly having T1DM or LADA.

u. A subject 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.

v. Subjects with elevated TG levels, who would qualify for a combined Visit 2/3/4, may be re-screened after being on a stable lipid-lowering regimen for at least 4 weeks. All other subjects (i.e., subjects who require Visits 2 and 3, prior to randomization at Visit 4) with elevated TG levels, may have lipid-lowering medication initiated or adjusted and continue in the trial if a repeat measurement (at Visit 3/Week -1) no longer meets the exclusion criterion. All subjects must be on a stable dose of a lipid-lowering medication for at least 4 weeks prior to Visit 4/Randomization (Day 1).

w. 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]). A subject with a positive urine pregnancy test during double-blind treatment period will interrupt sitagliptin, metformin, and insulin glargine treatment and undergo a serum pregnancy test.

x. 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.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 15 weeks before Visit 1/Screening.

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Assignment of Screening Number

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

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

Please refer to the Trial Flow Chart (see Section 6.0) and the Investigator Trial File Binder for specific details on the screening/rescreening visit requirements.

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

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

Adherence to treatment will be assessed by subject report during the double-blind treatment period. Every effort will be made to maintain adherence as close to 100% as possible.

Interruptions from the protocol specified treatment plan for ≥7 days OR compliance ≤75% require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of oral trial medication will be witnessed by the investigator and/or trial staff at Visit 4 or combined Visit 2/3/4, as applicable. LANTUS® will be administered by the subject in the evening and the site will call the subject on Day 2 to record the dose and timing of administration.

7.1.1.8.1 Diet and Exercise Counseling

Refer to Section 5.7 for further details.

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

At Visit 2 or Visit 4/Day 1 (as applicable to the subject) the site will dispense the Hypoglycemia Assessment Log (HAL) and review the symptoms and management of hypoglycemia with the subject. The site will counsel the subject to immediately perform a fingerstick glucose measurement if any symptoms occur that may be related to hypoglycemia (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), but also to avoid delay in treating these symptoms.

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

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

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

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

7.1.1.8.3 Dispense Glucose Meter and Self-Monitoring Blood Glucose (SMBG) Instructions

Glucose meters will be supplied to all subjects at Visit 2 or Visit 4/Day 1 (as applicable to the subject) in order to perform SMBG measurements. Subjects will be instructed on the procedure to perform fingerstick glucose measurements and document these measurements on the Fingerstick Glucose (FSG) Log. Subjects will monitor their fingerstick glucose concentrations at least once daily (fasting, 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 subject's risk for hypoglycemia or hyperglycemia). Additionally, beginning at Visit 4/Day 1, the daily insulin glargine (LANTUS®) dose will be recorded on the FSG Log. See further details regarding fingerstick measurements and insulin titration in Section 5.2.1.2.

Throughout the duration of the entire study (pre- and post-randomization), subjects will be instructed to contact the site if the fingerstick glucose values are ≤70 mg/dL (3.9 mmol/L). Post-randomization, the investigator will assess the potential need for a reduction in the insulin glargine (LANTUS®) dose based on the treat-to-target algorithm presented in Table 4 (see Section 5.2.1.2).

7.1.1.8.4 Medication Compliance Monitoring

All subjects will be directed to bring any used and unused bottles of double-blind study medication to each visit. The investigator must maintain a complete and current accountability record for the blinded study drug.

During the trial, compliance will be assessed by subject report (see Section 8.11). Every effort will be made to maintain compliance as close to 100% as possible.

The investigator or designee will counsel subjects who report taking <80% of the prescribed blinded study drug following randomization. The investigator or designee will determine the factors that resulted in <80% compliance with the blinded study drug and will take steps to improve compliance. Subjects will be counseled on the importance of taking their medication as prescribed. Subject counseling will be documented in source documents.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Vital Signs

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

Refer to the Investigator Trial File Binder for additional details regarding collection of vital signs measurements.

7.1.2.2 Physical Examination

7.1.2.2.1 Full Physical Examination

A full physical examination will be performed at the visits noted in the Trial Flow Chart - Section 6.0; genitourinary and rectal examination may be omitted from the full examination.

7.1.2.2.2 Brief Physical Examination

A brief physical examination including assessment of the heart, lungs, abdomen, extremities, and skin will be performed at the visits noted in the Trial Flow Chart - Section 6.0. Other body systems may be evaluated as per the judgment of the investigator or as needed to evaluate adverse events.

7.1.2.3 Height and Weight

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

Refer to the Investigator Trial File Binder for additional details regarding collection of height and weight measurements.

7.1.2.4 12-Lead Electrocardiogram (ECG)

A single, supine 12-lead ECG will be obtained at the visit noted in the Trial Flow Chart – Section 6.0.

- Subjects should avoid the ingestion of caffeine and nicotine-containing products for at least 30 minutes prior to the scheduled ECGs and blood pressure determinations.
- 12-lead ECGs should be performed after the subject has rested quietly for **at least 10 minutes** in a supine position.

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

The investigator is responsible for retaining all copies of the ECG reports.

7.1.2.5 Patient Telephone Contacts (PTCs)

Patient telephone contacts will be conducted according to the Trial Flow Chart - Section 6.0. The purpose of these phone calls is to assess insulin titration, monitor patients for hypoglycemia, and assess any adverse events which may have occurred since the previous clinic visit.

7.1.2.6 Continuous Glucose Monitoring (CGM)

Continuous Glucose Monitoring (CGM) will be conducted in all randomized subjects that agree to this procedure at **select** study sites at the visits noted in the Trial Flow Chart - Section 6.0.

CGM will be performed as described below in Table 5.

Table 5 Continuous Glucose Monitoring Schedule

Activity/Timepoint	Placement of Device/Sensor	Duration of Monitoring	Removal of Device/Sensor and Download of Data
Baseline	~1-2 Weeks Prior to Visit 4/Randomization (Day 1)	~1-2 Weeks	Visit 4/Randomization (Day 1)
Mid Study	Visit 6/Week 12	~1-2 Weeks	~1-2 Weeks after Visit 6/Week 12
End of Study	~1-2 Weeks Prior to Visit 9/Week 30	~1-2 Weeks	Visit 9/Week 30

Information on the precise timing and placement and removal of the sensor and device for CGM will be detailed in the Investigator Trial File Binder.

Sites will be required to transfer the downloaded data to the Sponsor's designee.

Please refer to the Investigator Trial File Binder for additional details.

7.1.3 Laboratory Procedures/Assessments

All laboratory tests outlined in the Trial Flow Chart - Section 6.0 will be performed by the central laboratory except for the following tests which will be performed at the investigational site: the optional site fingerstick A1C at Visit 1/Screening, the fasting fingerstick glucose measurement at the combined Visit 2/3/4 or Visit 4, Randomization (as applicable), dipstick urinalysis, and urine pregnancy tests.

Laboratory test results for chemistry, hematology, lipids, and FPG will not be masked. Hemoglobin A1C will be masked from the combined Visit 2/3/4 or Visit 4, Randomization (Day 1), as applicable, until study completion.

The central laboratory will flag the following safety measurements potentially meeting specific criteria for discontinuation from blinded study drug:

- eGFR <50 mL/min/1.73 m^2;
- elevations ≥3X ULN in liver transaminases (i.e., ALT and AST) (see Section 12.4 for guidance on retesting);
- positive serum pregnancy test.

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Refer to the Trial Flow Chart - Section 6.0 for specific laboratory tests performed at each trial visit.

7.1.3.1 Laboratory Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified below in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Others	Urinalysis
• Hemoglobin • Hematocrit • RBC Count • Platelet Count • WBC Count • Neutrophils • Eosinophils • Monocytes • Basophils • Lymphocytes	• BUN • Serum Creatinine (eGFR calculated using the MDRD formula) • Glucose • Sodium • Potassium • Chloride • Total Carbon Dioxide (Bicarbonate) • AST (SGOT) • ALT (SGPT) • Alkaline Phosphatase • Total Bilirubin • Direct (conjugated) Bilirubin[a] • Indirect (unconjugated) Bilirubin[a]	• TSH • Fasting C-peptide • A1C • FPG • Pregnancy Tests (where applicable) • Lipid Panel (i.e., Total Cholesterol, HDL-C, non-HDL-C, LDL-C, and Triglycerides)	• Blood • Glucose • Protein • Leukocyte esterase • Nitrates • Specific Gravity • Microscopic exam, if abnormal results are noted

[a] Both direct and indirect bilirubin measured only when total bilirubin is greater than ULN.

Laboratory tests will be performed after at least a 10-hour fast (i.e., no food, double-blind study drug, open-label AHA medication [metformin], or drink except water and non-AHA non-study drug as prescribed).

Subjects who have not fasted prior to Visit 1/Screening should return to the clinic fasting prior to Visit 4/Randomization for fasting TG and FPG measurements. After randomization, subjects who do not fast before a scheduled visit will be required to return fasting for the study visit within three days.

7.1.3.2 Future Biomedical Research Sample Collection

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

- Blood (DNA) for future research
- Plasma for future research
- Serum for future research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Discontinuation Visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.2 Blinding/Unblinding

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

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

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

7.1.4.3 Calibration of Critical Equipment

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

7.1.5 Visit Requirements

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

Refer to the Investigator Trial File Binder for details regarding the scheduling of study visits and patient telephone contacts.

7.2 Assessing and Recording Adverse Events

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

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

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

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

An overdose must be reported if either of the following occurs during the conduct of this trial: (1) Dosing of >400 mg/day of sitagliptin or sitagliptin-matching placebo or (2) >200 mg/day of sitagliptin or sitagliptin-matching placebo for more than 28 days. Investigators/site personnel are to consult the local approved insulin glargine (LANTUS®) and metformin (IR or XR) product labels for guidance on the definition of an overdose of these agents.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

7.2.4 Evaluating Adverse Events

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

Table 7 Evaluating Adverse Events

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 - 8.12.

Study Design Overview	Continuing sitagliptin vs. withdrawing sitagliptin when subjects initiate insulin and titrate insulin in a treat-to-target design
Treatment Assignment	Subjects will be randomized in a 1:1 ratio to continue sitagliptin or withdraw sitagliptin. Subjects will take sitagliptin and sitagliptin-matching placebo for the continuing sitagliptin group and withdrawing sitagliptin group, respectively. Stratification factor: AHA treatment at screening (Met + DPP-4i, Met + DPP-4i + SU, Met + SU)
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	• Change from baseline in A1C at Week 30 – Non-inferiority – Superiority • Event rate (number of events divided by follow-up time) of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) over 30 weeks
Key Secondary Endpoints	The following endpoints are included in the study objectives • Event rate of each of the following over 30 weeks – documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) – documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) – documented hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) • Incidence (number of subjects with ≥1 event divided by number of subjects) of each of the following over 30 weeks: – documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) – documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) – documented hypoglycemia with blood glucose ≤70 mg/dL

	(≤3.9 mmol/L) – documented hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) • Change from baseline in daily dose of insulin at Week 30 • Proportion of subjects with A1C goal <7.0% (<53 mmol/mol) at Week 30 • Proportion of subjects with A1C goal <7.0% (<53 mmol/mol) at Week 30 with no documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) during the study • Change from baseline in FPG at Week 30
Statistical Methods for Key Efficacy Analyses	The primary hypotheses for change from baseline in A1C at Week 30 will be assessed via a constrained longitudinal data analysis (cLDA) model. The primary hypothesis for event rate of symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) will be assessed using a negative binomial regression model [18].
Statistical Methods for Key Safety Analyses	There are no tier 1 safety endpoints. For Tier 2 endpoints, 95% confidence intervals will be provided for between-group differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method [19].
Interim Analyses	No interim analyses are planned.
Multiplicity	The study-wise type I error will be controlled at 0.05 using the graphical approach of Maurer and Bretz [20]. The primary hypothesis for A1C non-inferiority (H1A) will be tested first (at α=0.025, one-sided). If A1C non-inferiority is declared, the full α will be split equally and passed to the other 2 primary hypotheses; i.e., A1C superiority (H1B) and event rate of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (H2). The α allocated to H1B will be fully passed to H2 if the test for H1B is successful; and if the test for H2 is successful, the α finally allocated to H2 will be fully passed to the secondary hypotheses, which will be tested in a fixed sequence. The study will be declared successful if compared with withdrawing sitagliptin, continuing sitagliptin demonstrates non-inferior A1C reduction as well as at least one of the following: superior A1C reduction *or* reduction in the event rate of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L).
Sample Size and Power	The planned sample size is approximately 350 subjects per treatment group. The study will have >99% power to establish that compared with withdrawing sitagliptin, continuing sitagliptin is non-inferior for A1C reduction, and 93% power for A1C superiority, assuming that the underlying treatment difference is -0.3%. If A1C superiority is achieved, the study will have 93% power to detect a rate ratio of 0.6 for documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL at α=0.05; otherwise, the power will be 89% to detect the same ratio at α=0.025.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

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

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

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Sections 3.1 and 3.2. A non-inferiority margin of 0.3%, which is regarded as a minimum clinically relevant difference between 2 treatments, will be used for testing of the primary hypothesis for A1C. Non-inferiority will be declared if the upper bound of the two-sided 95% CI for the treatment effect (continuing sitagliptin minus withdrawing sitagliptin) is less than 0.3%.

8.4 Analysis Endpoints

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

For change from baseline parameters, the baseline value will be defined as the **Visit 4/Week 0/Day 1** (randomization) measurement. If the Visit 4 measurement is not available, the Visit 3/Week -1 measurement or Visit 1 measurement (only for subjects with a combined Visit2/3/4) will be used as baseline. If Visit 1 (only for subjects with a combined Visit 2/3/4), Visit 3, and Visit 4 measurements are not available, the baseline value will be treated as missing.

8.4.1 Efficacy Endpoints

The descriptions of the efficacy measurements and time points at which they are measured are described in Section 4.2.3.1 and Section 6.0 (Trial Flow Chart), respectively. The efficacy endpoints to be analyzed are listed in Table 8. These endpoints will be analyzed at or through Week 30.

Table 8 Efficacy Endpoints

Endpoints for the Primary Hypotheses
Change from baseline in A1C at Week 30 – Non-inferiority – Superiority
Event rate (number of events divided by follow-up time) of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) over 30 weeks
Endpoints for the Secondary Hypotheses
Event rate of documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L) over 30 weeks
Incidence (number of subjects with ≥1 event divided by number of subjects) of each of the following over 30 weeks – documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) – documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) – documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L)
Change from baseline in total daily insulin dose at Week 30
Other Key Secondary Endpoints
Event rate of the following over 30 weeks – documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) – documented hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L)
Incidence of document hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L)
Proportion of subjects at A1C goal <7.0% (<53 mmol/mol) at Week 30
Proportion of subjects at A1C goal <7.0% (<53 mmol/mol) at Week 30 with no documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L)
Change from baseline in FPG at Week 30

8.4.2 Safety Endpoints

Descriptions of the safety measurements and time points at which they are measured are provided in Section 4.2.3.2 and Section 6.0 (Trial Flow Chart), respectively. The safety endpoints to be analyzed are listed in Table 10 in Section 8.6.2. These endpoints will be analyzed over 30 weeks.

8.4.3 Derivation of Efficacy Endpoints

The event rate of a hypoglycemia endpoint for a subject is defined as the number of events divided by the follow-up time, which is the time from randomization to the end of the treatment period.

The daily insulin dose for any given post-randomization 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 subject 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 noninformative.

Definitions for weeks will be provided in the sSAP.

8.5 Analysis Populations

Summaries of subject disposition will include all randomized subjects. Summaries of baseline characteristics will be performed in the All Subjects Treated (AST) population, consisting of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group to which they were randomized for both of these populations.

8.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will be 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 subjects who received at least one dose of study treatment and had at least one measurement of the respective endpoint (baseline or post-baseline). Analyses in the FAS will exclude data after the last dose of study medication plus an offset of 5 days.

The intention-to-treat (ITT) population will be a secondary population for efficacy analyses. The ITT population will include the same subjects as FAS. However, analyses in the ITT population will include all available data, including data obtained after the last dose of study medication in subjects who remain in the study after discontinuing study medication.

A secondary population for the analysis of A1C goal <7.0% will be the AST population. This analysis will exclude data after the last dose of study medication plus an offset of 5 days.

Subjects will be included in the treatment group to which they are randomized for the efficacy analysis. Details on the approach to handling missing data are provided in Section 8.6, Statistical Methods.

8.5.2 Safety Analysis Populations

Analyses of safety in this trial will be performed in the All Subjects as Treated (ASaT) population, consisting of all randomized subjects who received at least one dose of trial treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data using the ASaT population. This will be the treatment group to which they were randomized with the exception of subjects who take incorrect study treatment for the entire treatment period. Such subjects will be included in the treatment group corresponding to the trial 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 are provided in Section 8.6, Statistical Methods.

8.6 Statistical Methods

Statistical testing and inference for efficacy analyses and safety analyses are described in Sections 8.6.1 and 8.6.2, respectively. The results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity.

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives related to the efficacy endpoints. Methods related to exploratory objectives will be described in the sSAP.

The primary estimands for the study consist of the following elements:

- Target population: patients with T2DM who have inadequate glycemic control on metformin and sitagliptin
- Endpoints:
    - mean change from baseline at Week 30
        - A1C
        - daily dose of insulin
    - event rate over 30 weeks
        - documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L)
        - documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L)
    - incidence over 30 weeks
        - documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L)
        - documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L] over 30 weeks
        - documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L)
- Measure of intervention effect: Difference (in means, in incidence) or ratio (of event rate) in the effect of randomized treatments (i.e., continuing sitagliptin vs. withdrawing sitagliptin) if all subjects followed the randomized treatment through Week 30.

For the primary analysis of change from baseline in A1C, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [21] will be used in the FAS population. 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 include terms for treatment, AHA treatment at screening (Met + DPP-4i, Met + DPP-4i + SU, Met + SU), time, and the interactions of time by treatment and of time by AHA treatment at screening. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The treatment difference in terms of mean change from baseline at Week 30 will be estimated and tested from this model. Continuing sitagliptin will be declared non-inferior to withdrawing

sitagliptin for A1C reduction if the upper limit of the two-sided 95% confidence interval (CI) for the mean difference at Week 30 is less than the non-inferiority margin, δ=0.3%. If non-inferiority is declared, then an assessment of superiority will be conducted following the multiplicity control strategy described in Section 8.8, Multiplicity.

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 analysis of covariance (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 subjects who are missing either the baseline or post-baseline measurements, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation code will be in the sSAP.

The cLDA method assumes that data are missing at random (MAR). In this study, it is expected that Missing at Random and Missing Completely at Random (MAR/MCAR) mechanisms will underlie most of the missingness, and the proportion of data missing not at random (MNAR), driven solely by unobserved values of the study endpoints, will be small. However, because the MNAR mechanism can never be ruled out, sensitivity analyses will be performed to assess the robustness of the conclusions from the cLDA analyses to departures from MAR:

- A sensitivity analysis will be performed for change from baseline in A1C with a pattern mixture model in conjunction with the tipping point approach [22], applicable to both the non-inferiority and the superiority hypotheses for change from baseline in A1C. With this method, missing values will be imputed based on the marginal univariate normal distributions with means equal to the predicted values and variances equal to the squared standard errors for the predicted values obtained from the cLDA assuming MAR. For each imputed value, a positive adjustment Δ_1 will be added for the continuing sitagliptin group (to the detriment of continuing sitagliptin). For each value of Δ_1, a negative adjustment Δ_2 will be added for the withdrawing sitagliptin group (to the improvement of withdrawing sitagliptin). The inference will be carried out for a range of values of Δ_1 and Δ_2, a two-dimensional adjustment. A contour plot will be constructed of values of Δ_1 and Δ_2 that render the significant result into non-significant, which provides a measure of robustness of the primary result.

- For the superiority hypothesis for change from baseline in A1C, a sensitivity analysis using a jump to reference (J2R) pattern mixture model will be performed [23].

  In this sensitivity analysis, the missing data due to dropout will be handled using J2R imputation, which falls under the category of pattern mixture models known as reference-based imputation. In J2R, missing data in the control group are imputed under the MAR assumption, while missing data in the treatment groups are imputed under a MNAR assumption using the control group profile for time points after withdrawal.

Standard multiple imputation techniques are overly conservative as they tend to overestimate parameter variances. Therefore, a more appropriate variance for the J2R based on pattern mixture model approximation [24] will be used. Details describing this methodology with relevant equations, model specifications, assumptions, and the SAS implementation code will be provided in the sSAP.

A detailed accounting of missing data will be provided, including a tabulation of the reasons for missingness (where known) and plots of the profile of mean A1C responses among subjects with different missingness patterns.

For the analysis of change from baseline in total daily insulin dose, a longitudinal data analysis (LDA) model will be used. The LDA model is similar to the cLDA model described above, except that the response vector consists of change from baseline at each post-baseline time point. The cLDA model will not be used for total daily insulin dose because the total daily insulin dose at baseline will be 10 units for all subjects following the study design.

For the analysis of change from baseline in FPG, the same cLDA model assuming MAR will be used.

For the analysis of percentages of individuals at the A1C goal of <7.0% (53 mmol/mol) at Week 30, the cLDA model under MAR for the change from baseline in A1C analysis will be used to impute the missing A1C values at Week 30. Imputations of the missing data will be based on the marginal univariate normal distributions with means equal to the predicted values and variances equal to the squared standard errors for the predicted values from the cLDA model. Ten sets of imputations of each missing value will be constructed from the cLDA model. Observed data will not be imputed. Subjects will be categorized as subjects at the A1C goal (satisfying the A1C specific goal of <7.0% [53 mmol/mol]) or subjects not at the goal at Week 30 after imputations.

To estimate the between-group rate difference, each of the 10 imputed data sets will be summarized to obtain the proportion of subjects at the goals within each group. The estimated proportions of subjects at the goals from the 10 imputed data sets will be combined using standard multiple imputation techniques proposed by Rubin [25] to yield an overall estimate of response rate and associated variance for each group. The estimated response rates and adjusted effective sample sizes [26] will then be used to obtain the confidence interval for between-group rate difference via M&N method [19], stratified by AHA treatment at screening.

In addition, as a sensitivity analysis the M&N method will be used to analyze the proportions of subjects at the A1C goal of <7.0% at Week 30 in the all subjects treated population, with missing data imputed as ‘not at goal’.

Hypoglycemia Endpoints

For hypoglycemia event rate and incidence rate analyses, categorization of episodes by glucose level will be performed based on the units (mg/dL or mmol/L) in which the glucose measurements were recorded.

To address the primary hypothesis related to hypoglycemia, the event rate of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L) in the continuing sitagliptin group will be compared with that of the withdrawing sitagliptin group. A negative binomial (NB) regression model with a log-link function will be used, with the number of events for each subject being the response variable. The model will include terms for treatment, race, region (i.e., North America, Europe, Other), AHA treatment at screening, baseline A1C value, baseline body weight, and an offset for follow-up time (on the natural log scale). The p-value and 95% CI for the ratio of event rates will be provided from the negative binomial regression model.

For hypoglycemia endpoints with blood glucose <56 mg/dL (≤3.1 mmol/L), it is expected that there will be a high proportion of subjects with no events. A zero-inflated negative binomial (ZINB) regression model will be fitted in addition to the NB model, as the ZINB model might provide a better fitting for count data with excessive zeros. The ZINB model supposes two data-generating mechanisms, one generating zeros and one generating the full range of counts. Under the ZINB model, the binary model component will include a term for treatment and will use a logit link function, and the negative binomial model component will include the same terms as included in the standard non-inflated NB model.

The Vuong test [27] will be used as the fit test for the ZINB model against the non-inflated NB model. If the p-value of the Vuong test is <0.10, the ZINB regression model will be the primary model. Because the ZINB model has interpretations for a subpopulation at risk and a non-susceptible subpopulation, a marginalized ZINB model will be utilized to test the treatment effect on the overall event rate.

In the event that there are outlying observations, i.e., the numbers of events for some subjects are substantially greater than expected and markedly deviate from the count data for other subjects, the maximum likelihood estimators of the NB or ZINB regression model parameters may be biased. The outliers may lead to overestimation of the standard errors and hence invalid inference. Thus, if the estimate of dispersion after fitting, as measured by Pearson's chi-square divided by the degrees of freedom, is greater than 1.25, then a robust M-estimator built to the primary regression model will be used for inference [28]. Details of the robust approach using M-estimation and sample SAS code will be provided in the sSAP.

The analysis of the incidence of documented hypoglycemia involved in the secondary hypotheses will use the M&N method. For subjects who discontinued from the study and had no hypoglycemia events prior to discontinuation, a proportional intensity model with Gamma frailty will be used to impute the missing hypoglycemia event data from discontinuation through the imputed Week 30 day, assuming missingness at random. The proportional intensity model will include the same terms as for the NB regression model. Imputation of the missing event data for each subject will be based on the estimated intensity function conditional on the observed event data. Ten sets of imputations for the number of events from discontinuation through Week 30 will be obtained from the intensity function. Based on the complete data after imputations, subjects will be categorized as having ≥1 event if the number of events during the entire 30-week treatment period is greater than 0; otherwise they will be categorized as having no events.

To estimate the between-group difference in incidence, each of the 10 imputed data sets will be summarized to obtain the proportion of subjects having at least one event within each group. The estimated proportions from the 10 imputed data sets will be combined using standard multiple imputation techniques proposed by Rubin [25] to yield an overall estimate of response rate and associated variance for each group. The estimated incidences and adjusted effective sample sizes [26] will then be used to obtain the confidence interval for between-group difference in incidence via M&N method, stratified by AHA treatment at screening.

The analysis of the proportion of subjects achieving A1C <7.0% at Week 30 with no documented hypoglycemia with blood glucose ≤70 mg/dL will use the M&N method in conjunction with MI for missing A1C and hypoglycemia data. The same imputation strategies will be used as described above.

Sensitivity analysis for the hypoglycemia related endpoints assuming MNAR will be performed. Details of the model specifications, assumptions, and SAS implementation code will be provided in the sSAP.

As glycemic control might confound the assessment of the treatment benefit of continuing sitagliptin versus withdrawing sitagliptin on hypoglycemia risk, a longitudinal count regression model may be implemented to adjust for the most recently measured A1C value as an exploratory analysis. The absolute hypoglycemia risk and risk ratio (continuing vs. withdrawing sitagliptin) controlling for A1C level will be assessed in relation to patient characteristics (e.g., race, sex, age) and A1C level. Details of the model specifications, assumptions, and SAS implementation code will be provided in the sSAP.

Analyses of the primary and key secondary endpoints will also be performed to address the intention-to-treat (ITT) estimand. The target population and endpoints for ITT will be the same as for the primary estimand. However, the measure of intervention effect for ITT will be the difference (or ratio) in means at Week 30 comparing randomized treatments plus other AHAs (if initiated) regardless of whether treatment continued to Week 30. Statistical methods for ITT will be the same primary methods used for the primary estimand.

Table 9 summarizes the key efficacy analyses.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint	Primary vs. Supportive Approach[†]	Statistical Method[‡]	Analysis Population	Missing Data Approach
Endpoints for Primary Hypotheses				
Change from baseline in A1C at Week 30 (non-inferiority)	P	cLDA	FAS	Model-based
	S	cLDA	FAS	PMM (tipping point)
	S	cLDA	ITT	Model-based
Change from baseline in A1C at Week 30 (superiority)	P	cLDA	FAS	Model-based
	S	cLDA	FAS	PMM (tipping point)
	S	cLDA	FAS	PMM (J2R)
	S	cLDA	ITT	Model-based
Event rate of documented symptomatic hypoglycemia with BG ≤70 mg/dL	P	NBR	FAS	DAO
	S	NBR	FAS	MI (MNAR)
	S	NBR	ITT	DAO
Endpoints for Secondary Hypotheses				
Incidence of documented symptomatic hypoglycemia with BG ≤70 mg/dL	P	M&N	FAS	MI (MAR)
	S	M&N	FAS	MI (MNAR)
	P	M&N	ITT	MI (MAR)
Event rate of documented symptomatic hypoglycemia with BG <56 mg/dL	P	NBR	FAS	DAO
	S	NBR	FAS	MI (MNAR)
	S	NBR	ITT	DAO
Incidence of documented hypoglycemia with BG ≤70 mg/dL	P	M&N	FAS	MI (MAR)
	S	M&N	FAS	MI (MNAR)
	S	M&N	ITT	MI (MAR)
Incidence of documented symptomatic hypoglycemia with BG <56 mg/dL	P	M&N	FAS	MI (MAR)
	S	M&N	FAS	MI (MNAR)
	S	M&N	ITT	MI (MAR)
Change from baseline in total daily insulin dose Week 30	P	LDA	FAS	Model-based
	S	LDA	FAS	PMM (J2R)
	S	LDA	ITT	Model-based
Other Secondary Endpoints				
Event rate of documented hypoglycemia with BG ≤70 mg/dL	P	NBR	FAS	DAO
Event rate of documented hypoglycemia with BG <56 mg/dL	P	NBR	FAS	DAO
Incidence of documented hypoglycemia with BG <56 mg/dL	P	M&N	FAS	MI (MAR)
Proportion of subjects with A1C < 7.0% at Week 30	P	M&N	FAS	MI
	S	M&N	AST	Missing=’not at goal’
Proportion of subjects with A1C <7.0% at Week 30 with no documented hypoglycemia with BG ≤70 mg/dL over 30 weeks	P	M&N	FAS	MI
Change from baseline in FPG at Week 30	P	cLDA	FAS	Model-based

Endpoint	Primary vs. Supportive Approach†	Statistical Method‡	Analysis Population	Missing Data Approach

† P=Primary approach; S=Supportive approach.
‡ For event rate endpoints with BG<56 mg/dL, ZINB will replace the standard non-inflated NB regression model if the p-value from the Vuong test is <0.10. Robust estimators will be used for inference if Pearson dispersion statistics is >1.25.
AST=All Subjects Treated; BG=Blood Glucose; cLDA=Constrained Longitudinal Data Analysis; DAO = Data as Observed; FAS=Full Analysis Set; FPG=Fasting Plasma Glucose; ITT=Intention to Treat; J2R=Jump to Reference; LDA=Longitudinal Data Analysis; MAR=missing at random; MI = Multiple Imputations; MNAR=missing not at random; M&N = Miettinen and Nurminen; NBR = Negative Binomial Regression; PMM = Pattern Mixture Model.

The strategy to address multiplicity issues with regard to multiple hypotheses is described in Section 8.8, Multiplicity.

8.6.2 Statistical Methods for Safety Analyses

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

The following analysis approaches will be used:

- The primary analysis approach will consider on-treatment data and data from the 14-day post-treatment follow-up.
- A secondary approach that applies only to AE summary measures, specific AEs, and serious AEs will include all data in the database after the first dose of double-blind study medication, with no exceptions.

The analysis of safety results will follow a tiered approach (Table 10). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences 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% confidence intervals provided for between-group comparisons. However, there are no "Tier 1" safety endpoints in this study. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group will be provided for Tier 3 safety parameters.

Adverse events (specific terms as well as system organ class terms) and predefined limits of change in laboratory, and vital signs 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 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change (defined in Section 12.5) will belong to Tier 3. For tier 2 events, 95% confidence intervals will be provided for between-treatment differences in the percentage of subjects with events using the M&N method.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have fewer than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE, and selected hypoglycemia endpoints will also be considered Tier 2 endpoints.

Continuous measures such as changes from baseline in laboratory and vital signs will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, summary statistics for the difference between treatment groups will also be provided, along with nominal p-values for between-group differences. Mean change from baseline over time will be plotted with the corresponding standard errors.

Table 10 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Discontinuation due to AE	X	X
	Selected hypoglycemia endpoints	X	X
	Specific AEs, SOCs, or PDLCs‡ (incidence ≥4 subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4 subjects in all of the treatment groups)		X
	Additional hypoglycemia endpoints		X
	Change from Baseline Results (Laboratory measurements, Vital Signs)		X

† Adverse Experience references refer to both Clinical and Laboratory AEs.
‡ Includes only those endpoints not already pre-specified as Tier-2 endpoints.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

Analysis of Hypoglycemia

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

- Documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L)
- Documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L)
- Documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L)

- Documented hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L)
- Severe hypoglycemia, defined as any episode of hypoglycemia that required assistance, either medical or non-medical, regardless of whether such assistance was obtained, and regardless of biochemical documentation. These events will be further sub-classified as:
  - Those that required medical assistance. Hypoglycemia episodes 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 required non-medical assistance to treat.
- Any hypoglycemia, regardless of biochemical documentation.

The Tier 3 summary will include the distribution of number of events per subject and event rate (calculated as the total number of events divided by the total patient-years of exposure) for the hypoglycemia endpoints listed above.

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

A listing including all episodes of hypoglycemia and a listing limited to severe hypoglycemia will be provided. For each episode, the associated glucose level, symptoms, severity, and precipitating factors will be presented in the listing.

8.6.3 Demographic and Baseline Characteristics

The comparability of the treatment groups 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 and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables. The following demographic/anthropometric, diabetes-related, and baseline efficacy variables will be summarized by treatment either by descriptive statistics or categorical tables. Depending on the variable of interest, statistics such as sample size, mean, SD, median, range and proportion will be provided.

- Continuous baseline demographic variables: age (years), weight (kg), height (cm), and body mass index (BMI; kg/m^2)
- Categorical baseline demographic variables: age, gender (male, female), and race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Multi-Racial), ethnicity (Hispanic/Latino or not)
- Baseline A1C, and distribution of A1C at baseline (A1C levels <8%, ≥8% and <9%, ≥9%)
- Baseline FPG
- Time since diagnosis of diabetes mellitus (years)
- Geographic region (North America, Europe, Other)

- AHA treatment at screening (Met + DPP-4i, Met + DPP-4i + SU, Met + SU).

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

8.7 Interim Analyses

No interim analyses are planned for this study.

8.8 Multiplicity

Figure 2 shows the multiplicity strategy for the overall control of type I error at 0.05 level, using the graphical approach of Maurer and Bretz [20]. All tests will be two-sided, except that a one-sided test will be conducted for A1C non-inferiority.

Among the 3 primary hypotheses including A1C non-inferiority (H1A), A1C superiority (H1B), and event rate for documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (H2), H1A will be tested first (at α=0.025, one-sided). If the test for H1A is successful and A1C non-inferiority is declared, then the full α=0.05 (two-sided) will be split in half (with weights, ω, equal 0.5 for both) and passed to H1B and H2. If the test for H1B is successful, the α allocated to H1B will be fully passed to H2. If the test for H2 is successful, the α finally allocated to H2 will be fully passed to the secondary hypotheses. That is, if the test for H2 but not H1B is successful, the α passed onto the secondary hypotheses will be 0.025. If the tests for both H1B and H2 are successful, the α passed onto the secondary hypotheses will be 0.05.

The study will be declared successful if the test for H1A is successful as well as H1B **or** H2; that is, if compared with withdrawing sitagliptin, continuing sitagliptin demonstrates non-inferior A1C reduction plus superior A1C reduction or reduction in the event rate of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL.

The secondary hypotheses will be tested in a fixed sequence in the following order, using the α level that was used for testing H2:

- Incidence of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L)
- Event rate of documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L)
- Incidence of documented hypoglycemia with blood glucose ≤70 mg/dL (≤3.9 mmol/L)
- Incidence of documented symptomatic hypoglycemia with blood glucose <56 mg/dL (≤3.1 mmol/L)
- Change from baseline in total daily insulin dose.

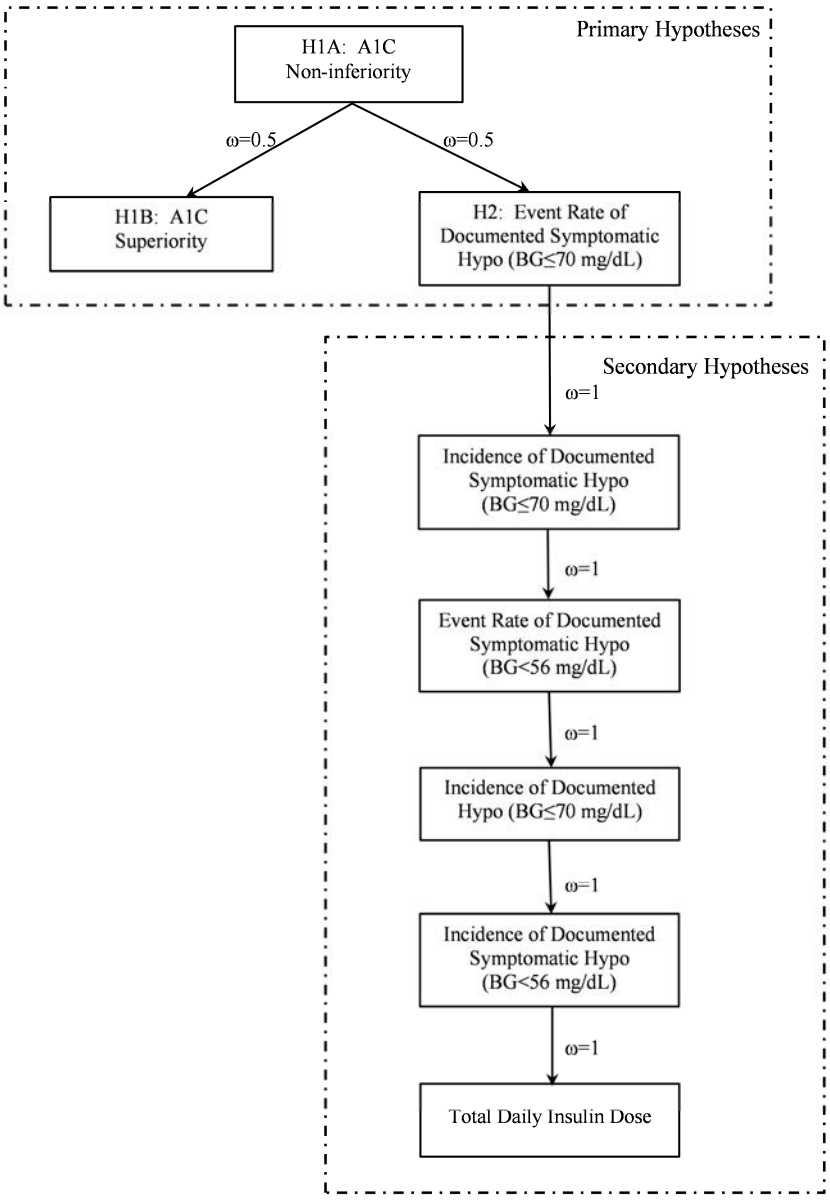


Figure 2 Multiplicity Strategy

8.9 Sample Size and Power Calculations

8.9.1 Sample Size and Power for Change from Baseline in A1C

The study will randomize approximately 700 subjects (in a 1:1 ratio) into the continuing sitagliptin and withdrawing sitagliptin groups.

With the planned sample size, this study will provide >99% power to establish that continuing sitagliptin is non-inferior to withdrawing sitagliptin in lowering A1C at α=0.025 level (one-sided), assuming an underlying treatment difference of -0.3%. The power and sample sizes are based on the following assumptions derived from the insulin-sparing study (MK-0431 P260) and two metformin add-on studies in the sitagliptin program (MK-0431 P024 and MK-0431 P803):

1) The cumulative attrition rates for each treatment group at Weeks 6, 12, 18, 24, 30 are 0.06, 0.08, 0.11, 0.14, and 0.20.

2) The conditional correlation matrix at Weeks 6, 12, 18, 24, and 30 is:

1.0	0.8	0.7	0.6	0.6
0.8	1.0	0.8	0.7	0.7
0.7	0.8	1.0	0.9	0.8
0.6	0.7	0.9	1.0	0.9
0.6	0.7	0.8	0.9	1.0

3) A conditional standard deviation of 1.0%.

The calculation is based on the two-sample t-test with an effective sample size of 311 subjects per group and was carried out using SAS v9.3. The minimum criterion for success is that the upper bound of the two-sided 95% CI of the difference is less than 0.3% (before rounding). Given the assumed SD of changes from baseline in A1C, the half-width of the 95% CI for the between-group difference (continuing vs. withdrawing sitagliptin) is expected to be 0.16%; thus, if the observed between-group difference is less than 0.14%, the success criterion for non-inferiority will be met.

For the A1C superiority hypothesis, at α=0.025 (two-sided), the study will have 93% to declare that continuing sitagliptin is superior to withdrawing sitagliptin in A1C-lowering, if the underlying (continuing sitagliptin minus withdrawing sitagliptin) between-group difference is -0.30%.

Table 11 shows the power for A1C superiority under different assumptions.

Table 11 Power (%) for A1C (%) Superiority Under Various Assumptions

α-level	True Difference	Conditional Standard Deviation	Power (%)	97.5% CI Half-Width
0.025	-0.30	1.0	93	0.18
	-0.25	1.0	81	0.18
	-0.30	0.9	97	0.16
	-0.25	0.9	89	0.16

For symptomatic hypoglycemia with blood glucose ≤70 mg/dL, a rate ratio of 0.5 was observed in MK-0431 P260 (the insulin-sparing study). A sample size of 350/group will provide 89% power to detect a rate ratio of 0.6 for at α=0.025 and 93% power at α=0.05.

Table 12 shows the power for this endpoint under different assumptions and at α-level of 0.025 and 0.05.

Table 12 Power for Event Rate of Symptomatic Hypoglycemia with Blood Glucose ≤70 mg/dL

α-level	Event Rate (number of events per patient per day) (withdrawing sitagliptin)	Rate Ratio (continuing vs. withdrawing)	Power (%)
0.025	0.02	0.50 0.60 0.65	>99 89 76
0.05	0.02	0.50 0.60 0.65	>99 93 84

Table 13 below shows the projected power for endpoints in the primary and secondary hypotheses following the order of testing as specified in Section 8.8, Multiplicity.

Table 13 Summary of Power (%) for Endpoints in Primary and Secondary Hypotheses

Endpoints for the Primary Hypothesis	**Marginal Power**	
	α=0.05	**α=0.025**
Change from baseline in A1C at Week 30 (non-inferiority)	>99%	–
Change from baseline in A1C at Week 30 (superiority)	–	93%
Event rate of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL over 30 weeks	93%	89%
Endpoints for the Secondary Hypotheses		
Incidence of documented symptomatic hypoglycemia ≤70 mg/dL over 30 weeks	88%	82%
Event rate of documented symptomatic hypoglycemia <56 mg/dL over 30 weeks	81 to 96%	72 to 93%
Incidence of documented hypoglycemia ≤70 mg/dL over 30 weeks	86%	79%
Incidence of documented symptomatic hypoglycemia <56 mg/dL over 30 weeks	84%	77%
Change from baseline in total daily insulin dose at Week 30	84%	77%

8.10 Subgroup Analyses and Effect of Baseline Factors

To assess whether the treatment effect at Week 30 is consistent across various subgroups, point estimates and 95% CIs for the between-group difference for the change from baseline in A1C and ratio of the event rate of symptomatic hypoglycemia with blood glucose ≤70 mg/dL will be provided within each category of the following classification variables:

- Baseline A1C levels (<9.0%, ≥9.0%)
- Age categories (<65 years old, ≥65 years old)
- Sex (female, male)
- Region (North America, Europe, Other)
- AHA treatment at screening (Met + DPP-4i, Met + DPP-4i + SU, Met + SU).

No p-values will be provided for assessing treatment-by-subgroup interaction.

The consistency of the treatment effect in A1C will be assessed in the context of a repeated measures ANCOVA (RM ANCOVA) method, which is a generalization of the standard ANCOVA to accommodate repeated measurements. The RM ANCOVA model will include terms for treatment, AHA treatment at screening, baseline value for A1C, subgroup, and treatment-by-subgroup interaction. Time is treated as a categorical variable and time-specific versions of each term listed above at each week will be used to acknowledge the repeated nature of the measurements. An unstructured covariance matrix will be used to model the correlation among repeated measurements. For subgroup analyses based on factors that are already in the main model, the respective term will appear in the model only once. Treatment effects and nominal 95% confidence intervals by category for the classification variables listed above will be reported as well as presented graphically. Formal statistical testing of treatment-by-subgroup interactions will not be performed.

The consistency of the treatment effect in the event rate of documented symptomatic hypoglycemia with blood glucose ≤70 mg/dL will be assessed using a negative binomial model, with terms for treatment, baseline value for A1C, baseline body weight, AHA treatment at screening, race, region, subgroup, and treatment-by-subgroup interaction, and an offset for time of follow-up (on a natural log scale). For subgroup analyses based on factors that are already in the main model, the respective term will appear in the model only once. Treatment effects and nominal 95% confidence intervals by category for the classification variables listed above will be reported as well as presented graphically.

8.11 Compliance (Medication Adherence)

The computation of compliance in the AST population will be based on the study medication case report form. Both the assigned treatment and any matching placebo tablets will be included in the compliance calculation.

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

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

A day within the Double-blind Treatment period will be considered a compliant day if the subject was compliant with study medication on that day, i.e., if the subject took exactly one 1 tablet of sitagliptin 100 mg or sitagliptin-matching placebo.

If the study medication eCRF indicates general compliance problems with any blinded therapy, the subject will be considered non-compliant for that day regardless of the number of tablets reported.

The "Number of Days in Double-blind Treatment Period" is defined for each subject as the total number of days from the first dose of double-blind study medication to the last day of study medication for sitagliptin or sitagliptin-matching placebo.

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

8.12 Extent of Exposure

The extent of exposure to double-blinded study treatment will be evaluated by summary statistics (N, mean, median, standard deviation and range) and frequencies for the "Number of Days on Therapy" by treatment group, based on daily dosing records on the study medication eCRF.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 14.

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

Table 14 Product Descriptions

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

All placebos were created by the Sponsor to match the active product.

All other supplies not indicated in Table 14 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

9.2 Packaging and Labeling Information

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

Subjects switching from another DPP-4 inhibitor or a sulfonylurea to sitagliptin at Visit 2 will receive open-label supplies in finished good bottles containing 63 Sitagliptin 100 mg tablets.

All subjects will receive double blind supplies every 6 weeks throughout the 30-week double blind treatment period in finished good bottles containing either 50 sitagliptin tablets or 50 sitagliptin-matching placebo tablets.

9.3 Clinical Supplies Disclosure

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

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

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.2 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox PPD and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

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

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

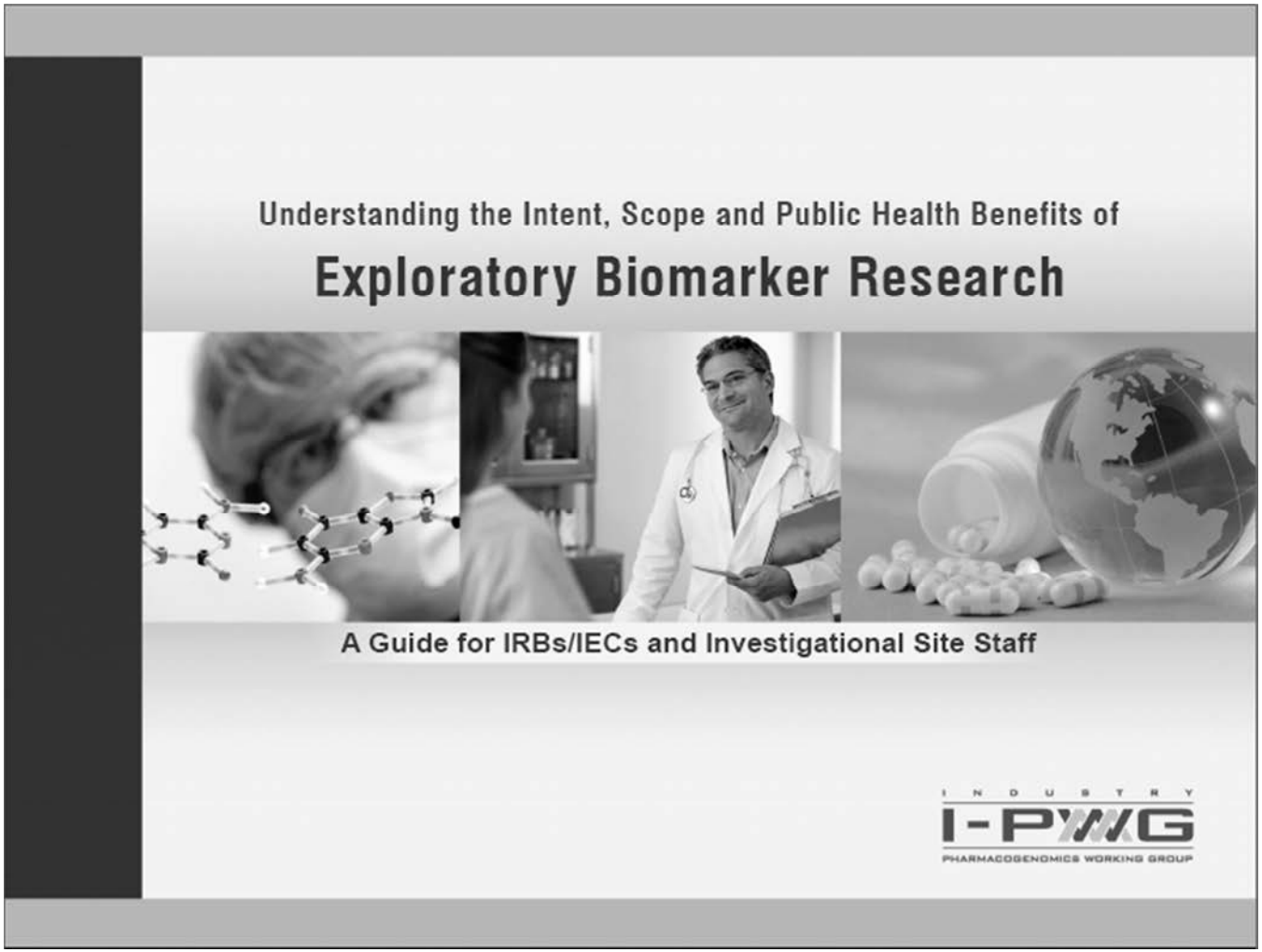
12. Questions

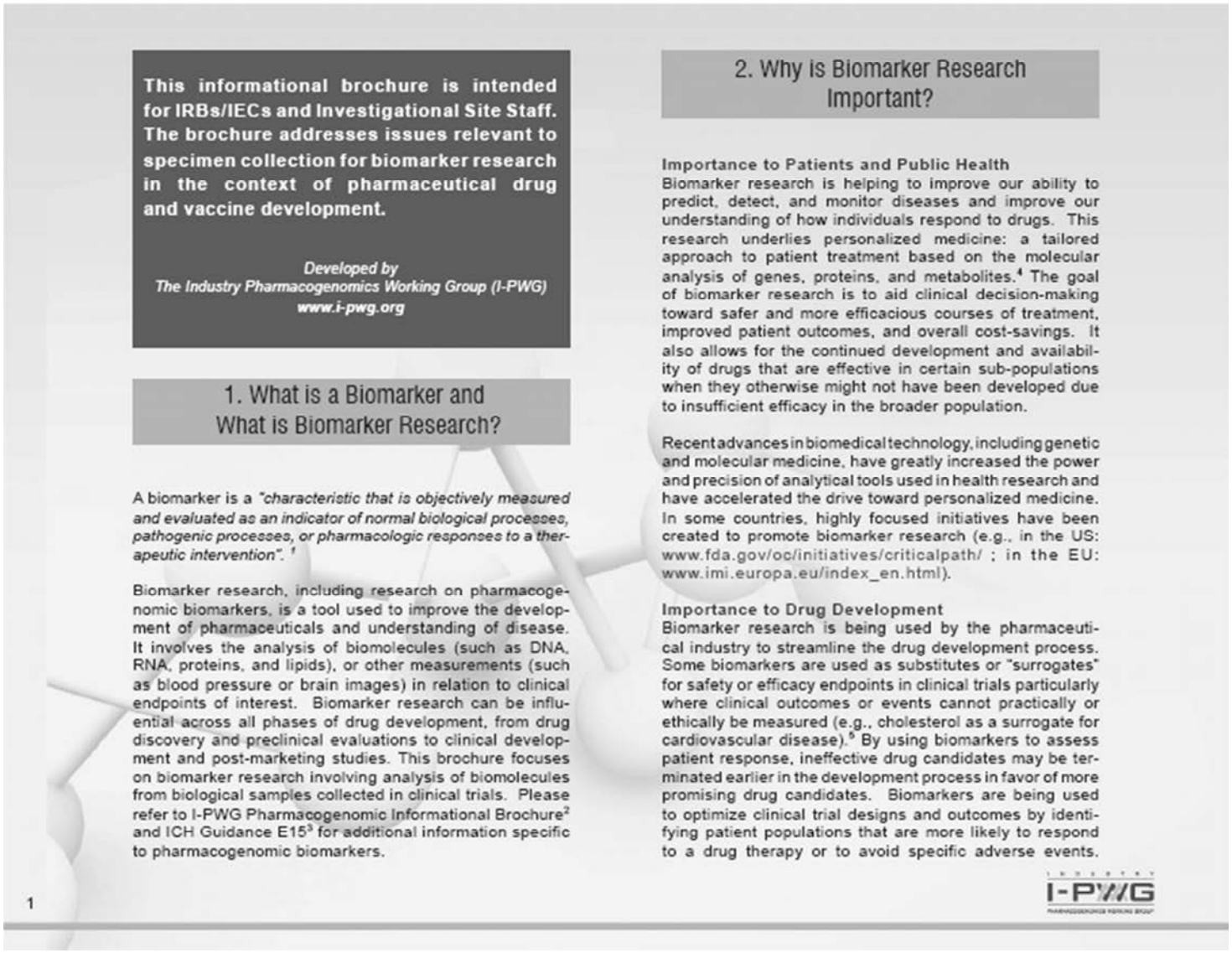
Any questions related to the future biomedical research should be e-mailed directly to PPD

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

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





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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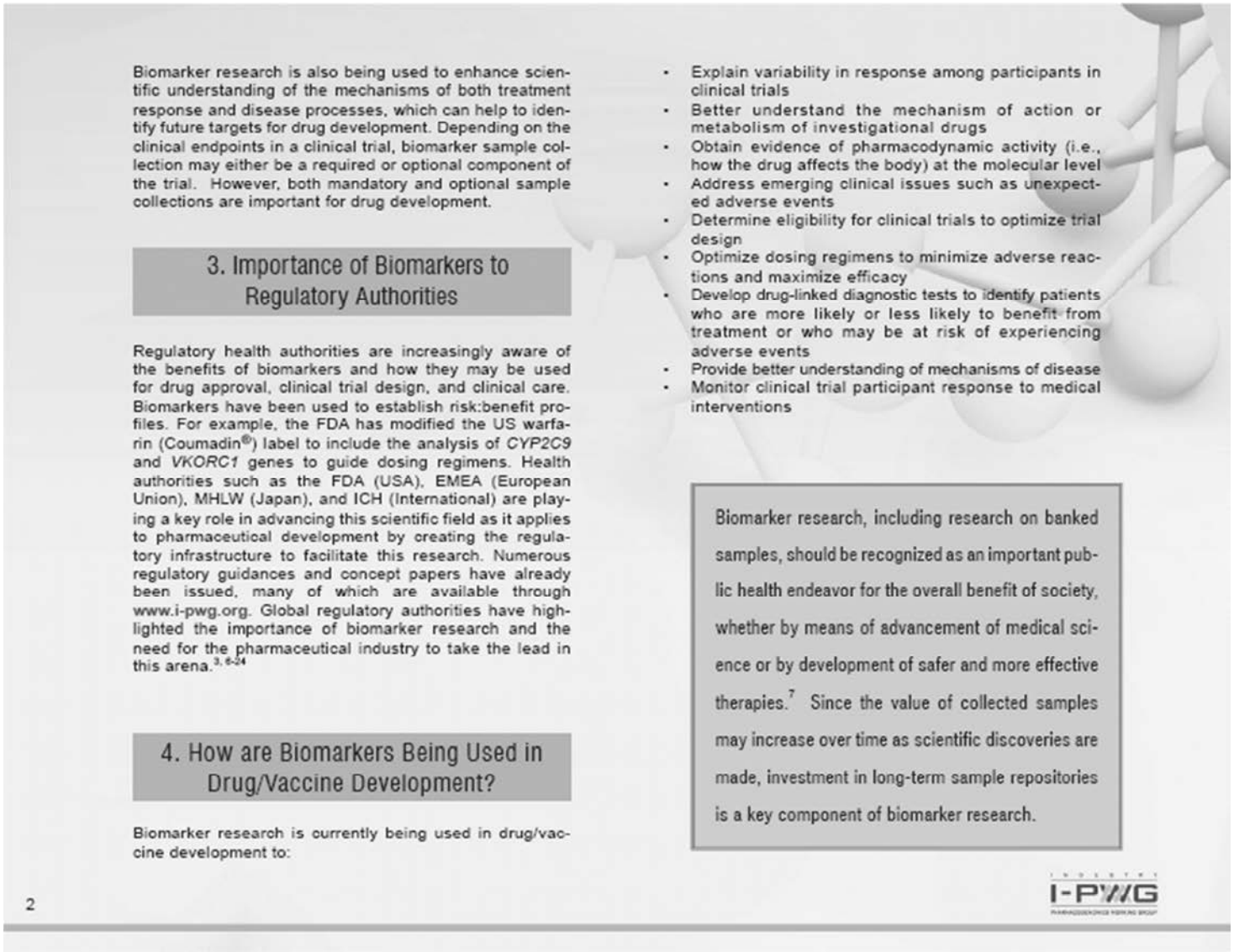
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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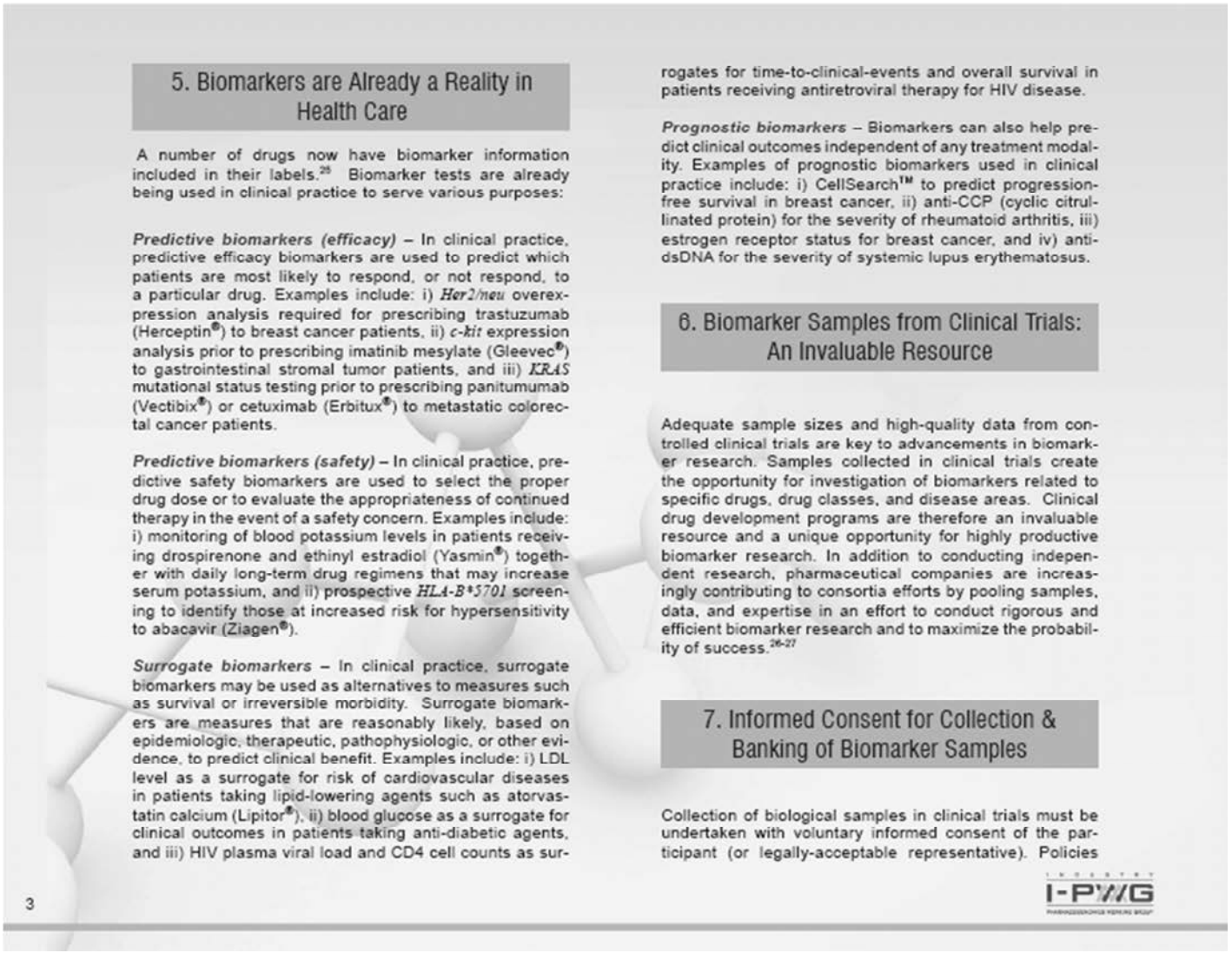

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[26-31]

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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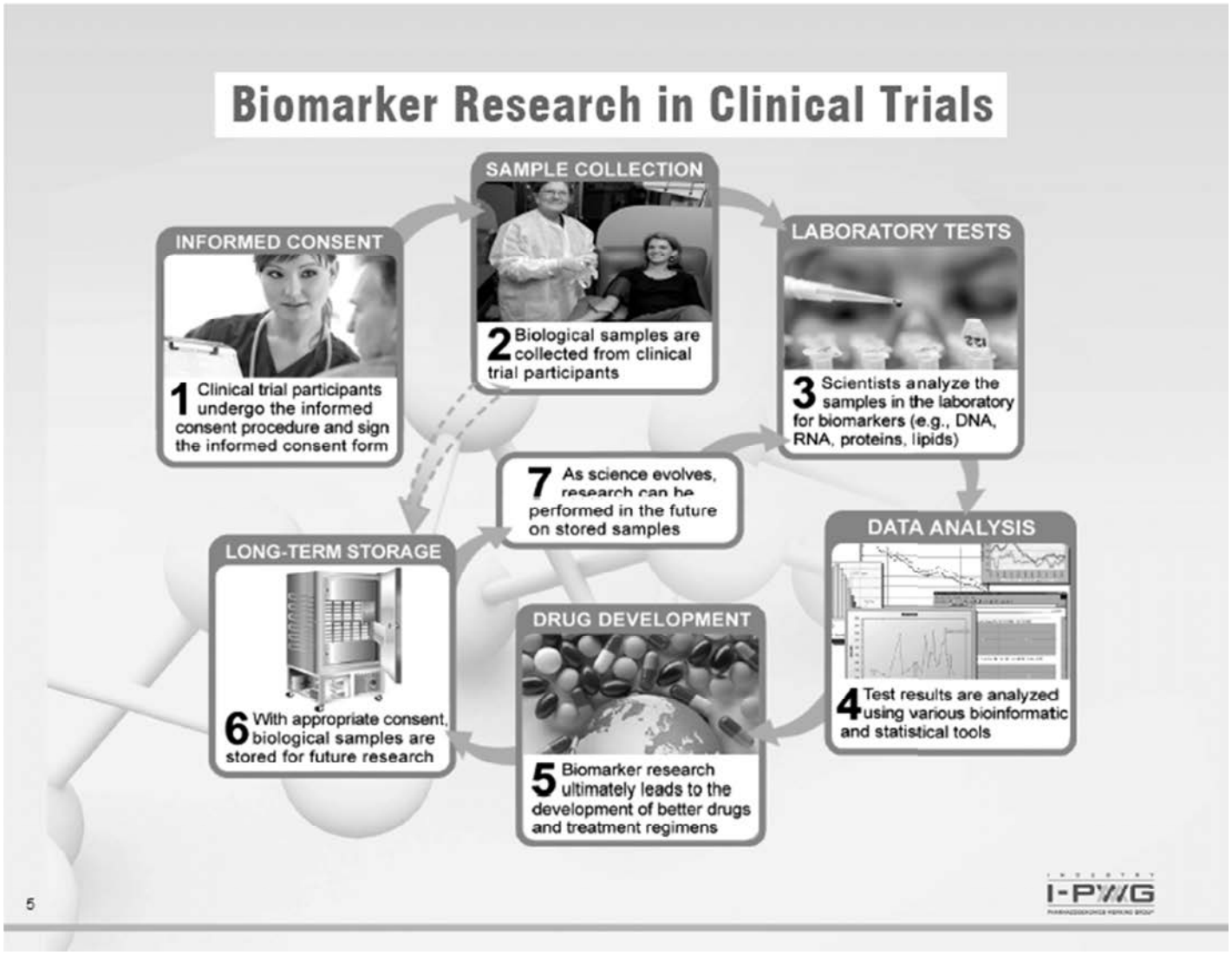
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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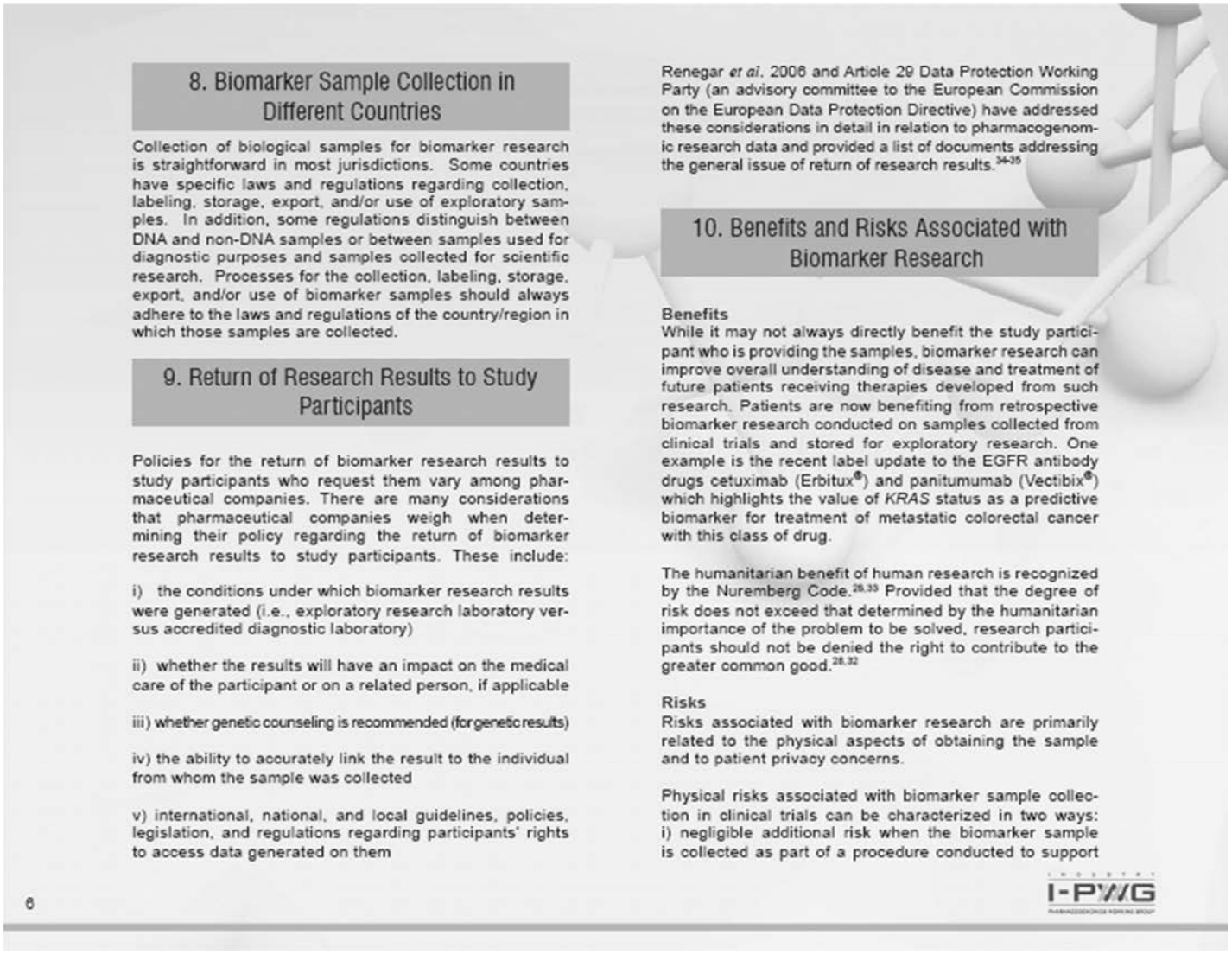
8. Biomarker Sample Collection in Different Countries
Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.
9. Return of Research Results to Study Participants
Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:
i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)
ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable
iii) whether genetic counseling is recommended (for genetic results)
iv) the ability to accurately link the result to the individual from whom the sample was collected
v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them
Renegar et al. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]
10. Benefits and Risks Associated with Biomarker Research
Benefits
While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of KRAS status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.
The humanitarian benefit of human research is recognized by the Nuremberg Code.[26,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[26,32]
Risks
Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.
Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support
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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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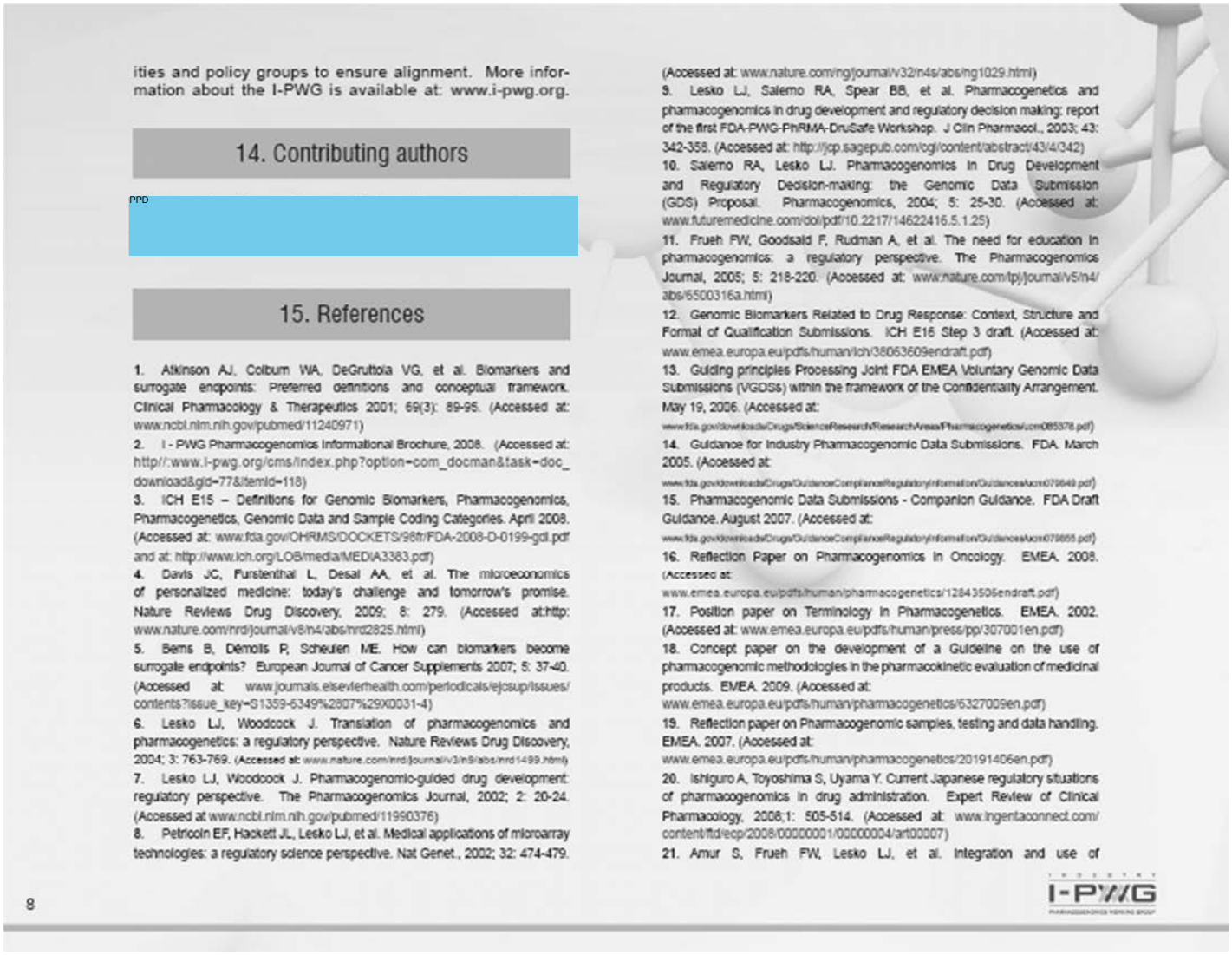

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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12.4 Management of Subjects with Elevated Liver Function Tests

Section I: Identification and Management of Subjects with ALT or AST Results ≥3X ULN

Increases in ALT or AST ≥ 3X the upper limit of normal (ULN) will be assessed in this study according to the procedures described below. The central laboratory report will alert the investigator if a subject meets this threshold. When a randomized subject who is receiving blinded study drug has an ALT or AST elevation ≥ 3X ULN, the investigator should determine which set of criteria the subject meets from the table below, based upon the following factors: (1) the magnitude of the subject's ALT or AST elevation, (2) the presence or absence of signs and symptoms, and (3) whether there is a corresponding increase in total bilirubin (TBL) ≥2X ULN. The investigator should monitor the subject and determine whether to interrupt study drug, in accordance with the instructions relevant to the specific criterion met.

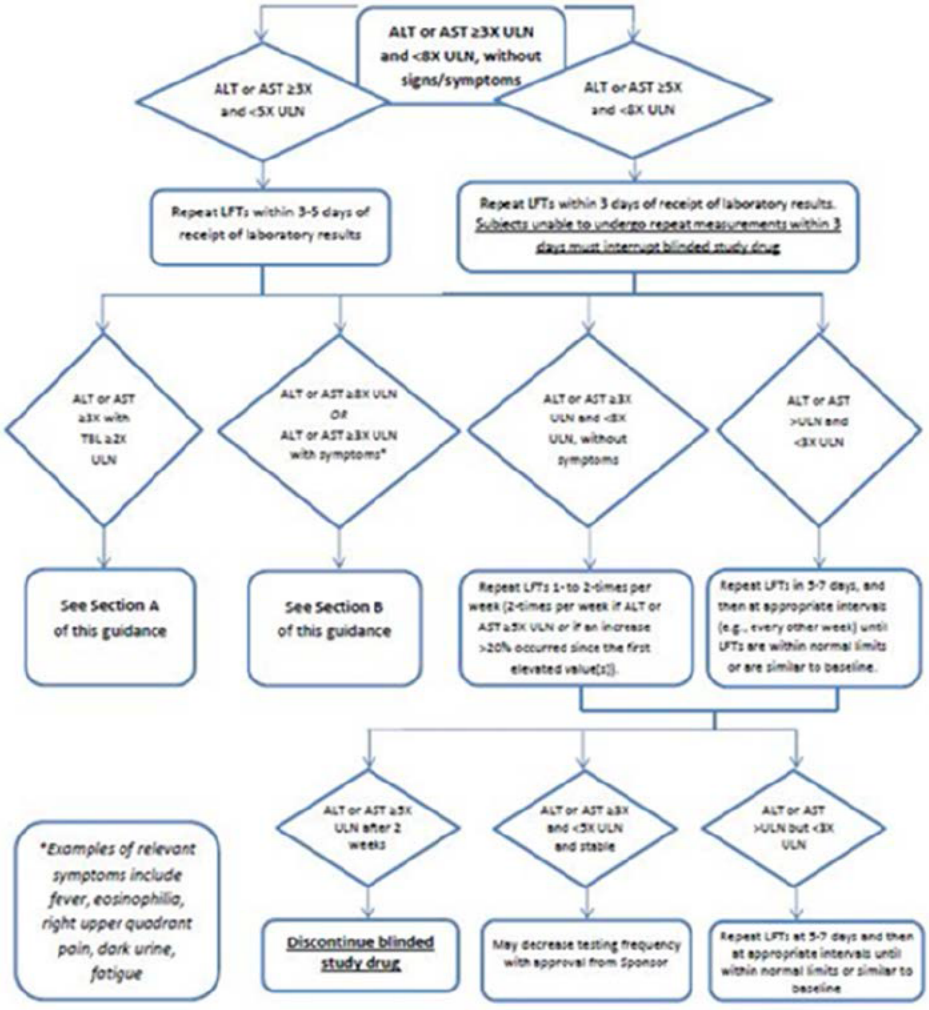
Investigator Instructions for Management of Subjects with ALT or AST ≥3X ULN

A) Subject has: • **ALT or AST ≥3X ULN with TBL ≥2X ULN and alkaline phosphatase <2X ULN**
1. The subject should *interrupt* blinded study drug. 2. Refer to the "*Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials*" (located in the Investigator Trial File Binder or equivalent) and perform procedures accordingly. 3. If an etiology for the elevated ALT or AST and TBL levels is established and the abnormalities resolve, blinded study drug may be restarted with approval by the Sponsor. Otherwise, the subject should discontinue treatment with blinded study drug. **Note:** Laboratory assessments prescribed in the *Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials* may be sent locally in emergent cases and to support subject compliance with the necessary evaluations. Subjects unwilling or unable to undergo the prescribed testing should be discontinued from treatment with blinded study drug.

B) Subject has: • **ALT or AST ≥8X ULN** ***OR*** • **ALT or AST ≥3X ULN and <8X ULN, with signs or symptoms of a drug reaction consistent with liver injury (e.g., fever, eosinophilia, right upper quadrant pain, dark urine, fatigue, etc.)**
1. The subject should *interrupt* blinded study drug. 2. Perform repeat ALT and AST within 3 days of receipt of the laboratory report. 3. Initiate evaluation for potential causes. See Section II below. 4. Repeat ALT and AST tests at appropriate intervals, initially approximately 2-times per week, until resolution or return to baseline. 5. If an etiology for the elevated liver enzymes is established (e.g., active hepatitis with specific etiology demonstrated, cholecystitis, biliary obstruction), blinded study drug may be restarted with approval by the Sponsor. Otherwise, the subject should discontinue treatment with blinded study drug. **Note:** Local laboratory assessments can be used to support compliance with the repeat testing procedure described above if required. Subjects unwilling or unable to undergo repeat ALT and AST testing at the frequency recommended above should be discontinued from treatment with blinded study drug.

C) Subject has:

- **ALT or AST ≥3X and <8X ULN, without associated signs or symptoms**



In summary, subjects should be discontinued from blinded study drug for any of the following reasons:

- ALT or AST ≥3X ULN with TBL ≥2X ULN and alkaline phosphatase <2X ULN and without an established etiology
- ALT or AST ≥8X ULN or ≥3X ULN with symptoms consistent with liver injury and without an established etiology
- ALT or AST ≥5X ULN for 2 weeks

Section II: Guidance for Assessment of Potential Etiology

Questions to Assess Etiology

Investigate potential causes for the subject's elevated liver enzymes using the questions below. Answers to the questions should be recorded in the subject's source documents and appropriate eCRFs.

1. Has the subject recently:

    - Had a change in his/her pattern of alcohol use? Investigate historic pattern of alcohol use as well.
    - Administered an illegal drug(s) (including intravenous drugs)?
    - Been exposed to a chemical agent or other environmental toxin?
    - Consumed any unusual foods (e.g., mushrooms), seasonal foods, or initiated treatment with new herbal/nutritional supplements?
    - Initiated a new diet regimen, started a rigorous exercise program, or experienced any form of severe physical exertion?
    - Traveled to another country or region?

2. Does the subject have a relevant concomitant illness (e.g., cholelithiasis, hepatitis, etc.) or has the subject had potential exposure to viral hepatitis (transfusion, tattoo, new sexual partner)?

3. Does the subject have a relevant medical history (e.g., autoimmune disorder, cancer, Gilbert's syndrome, obesity, Wilson's disease, NASH, alcoholic or infectious hepatitis, biliary tract disease, hypoxic/ischemic hepatopathy, etc.)?

4. Has the subject recently been treated with a concomitant medication(s) with demonstrated or suspected effects on the liver (e.g., acetaminophen; amiodarone; aspirin; chlorpromazine; dantrolene; erythromycin; halothane; isoniazid; methyldopa; nitrofurantoin; oxyphenisatin; perhexiline maleate; phenytoin; propylthiouracil; rifampin; sulfonamides; tetracyclines) or initiated treatment with another new medication(s)?

Additional Laboratory/Imaging Evaluations

In subjects for whom an etiology for the abnormal liver enzymes is unknown or whose elevated liver enzymes persist for more than 1 week:

1. Consider performing serologic tests including: (a) Hepatitis A (IgM); (b) Hepatitis B (surface antigen and core IgM); (c) Hepatitis C (antibody); (d) Hepatitis E (IgG and IgM). Obtain consent prior to testing, if required locally. Additional evaluations may be performed at the discretion of the investigator.

2. Consider an ultrasound of the subject's right upper quadrant and additional scans (endoscopic retrograde cholangiopancreatography [ERCP] or magnetic resonance cholangiopancreatography [MRCP]) if needed.

Note: Subjects may also be referred to a gastroenterologist or hepatologist for an additional work-up if considered necessary by the investigator.

12.5 Predefined Limits of Change (PDLC)

The following predefined limits of change will be assessed in the statistical analysis, as described in Section 8.6.2.

Laboratory Test	Predefined Limits of Change† Criteria	Categories Assessed for Each Criteria	
		At least One Value	Last On-Treatment Value
Laboratory – Chemistry			
Serum Creatinine (mg/dL)	1. Increase ≥0.3 mg/dL	N	Y
Total Bilirubin (mg/dL)	2. Value ≥2×ULN	Y	Y
AST (IU/L)	1. Value ≥3×ULN	Y	Y
ALT (IU/L)	1. Value ≥3×ULN	Y	Y
AST (IU/L) or ALT (IU/L)	1. Value ≥3×ULN	Y	Y
AST (IU/L) or ALT (IU/L)+ Total Bilirubin (mg/dL)	1. ALT ≥3×ULN or AST ≥3×ULN with Bilirubin ≥2×ULN	Y	Y
Alkaline Phosphatase (IU/L)	1. Value >1.5×ULN	Y	Y

† Increases and decreases are relative to baseline.
LLN = Lower limit of normal; ULN = Upper limit of normal.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	