

<b>Official Protocol Title:</b>	A Phase III, Multicenter, Randomized, Double-Blind, Active-Comparator Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Sitagliptin Compared with the Addition of Dapagliflozin in Subjects with Type 2 Diabetes Mellitus and Mild Renal Impairment Who Have Inadequate Glycemic Control on Metformin With or Without a Sulfonylurea
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**TITLE:**

A Phase III, Multicenter, Randomized, Double-Blind, Active-Comparator Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Sitagliptin Compared with the Addition of Dapagliflozin in Subjects with Type 2 Diabetes Mellitus and Mild Renal Impairment Who Have Inadequate Glycemic Control on Metformin With or Without a Sulfonylurea

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**SUMMARY OF CHANGES**

**PRIMARY REASON(S) FOR THIS AMENDMENT:**

Section Numbers	Section Titles	Description of Change s	Rationale
1.0 2.1 2.2 3.1 3.2 4.2.1 5.1.1 5.1.2 5.1.3 5.2 5.2.1.2.3 5.2.2 5.5 5.7	Protocol Title Trial Summary Trial Design Trial Diagram Primary Objectives & Hypotheses Secondary Objectives & Hypotheses Rationale for the Trial and Selected Subject Population Diagnosis/Condition for Entry into the Trial Subject Inclusion Criteria Subject Exclusion Criteria Trial Treatment Dose Modification of Metformin and Sulfonylurea Timing of Dose Administration Concomitant Medications/Vaccinations (Allowed & Prohibited) Subject Withdrawal/Discontinuation Criteria	Visit 1: expanded the population to include subjects on dual combination with metformin and an SU agent	Since both sitagliptin and dapagliflozin are commonly used in dual combinations (e.g., add-on to metformin) and in triple combinations (e.g., add-on to metformin and an SU agent), the background allowed AHAs will be expanded to include patients on either metformin monotherapy or metformin in dual combination with an SU agent. This will better reflect the breadth of add-on uses of both dapagliflozin and sitagliptin, and therefore allow a more robust comparison of these agents. The dose of the SU agent will be required to be at least 50% of maximum labeled dose, consistent with near maximum efficacy of the SU agent.

6.0	Trial Flow Chart		
7.1.2.11	Mixed Meal Tolerance Test (MMTT)		
7.1.3.1	Laboratory Evaluations (Hematology, Chemistry and Others)		
7.1.5.1	Fasting Prior to Scheduled Visits		
7.1.5.2	Scheduling Visits		
7.1.5.3	Visit 1/Screening		
8.1	Statistical Analysis Plan Summary		
8.5.1	Efficacy Analysis Populations		
8.6.1	Statistical Methods for Efficacy Analyses		
8.6.2	Statistical Methods for Safety Analyses		
8.6.3	Demographic and Baseline Characteristics		
2.1	Trial Design	Visit 1: Increased the upper limit of the A1C range to 9.5% from 9.0%	This allows a broader range of patients to participate, including patients (i.e., those between 9-9.5% A1C values) who would often receive the addition of therapy with sitagliptin or dapagliflozin.
5.1.2	Inclusion Criteria		
5.1.2	Inclusion Criteria	Visit 1: Added criteria that will allow subjects to qualify for a repeat test of their Visit 1 eGFR.	To allow patients with previous eGFR values (prior to study entry) within protocol-specified ranges, who do not meet required eGFR range at Screening, to have a single repeat.

<p>5.1.2</p> <p>2.2</p>	<p>Inclusion Criteria</p> <p>Trial Diagram</p>	<p>Visit 2: Updated the eGFR inclusion criteria and expanded the criteria required for subjects to qualify for a repeat test of their Visit 2 eGFR.</p> <p>Added the modified Visit 2 eGFR inclusion criteria.</p>	<p>To simplify the Visit 2 eGFR entry criteria: allowing patients with changes in eGFR within the range of day-to-day variability (<math>\leq 20</math> mL/min/1.73 m<sup>2</sup> compared to the Visit 1 qualifying value) to participate, if eGFR is still in protocol-specified eGFR range (i.e., 60-90 mL/min/1.73 m<sup>2</sup>). Also, to allow patients with eGFR values slightly outside of the range of day to day variability (up to <math>\leq 30</math> mL/min/1.73 m<sup>2</sup> compared to the Visit 1 qualifying value) to have a single repeat to evaluate eligibility.</p>
<p>5.1.3</p>	<p>Exclusion Criteria</p>	<p>Added note to state that subjects that were excluded based upon Protocol 838-00, but may be eligible under Protocol 838-02, may be rescreened, one time.</p>	<p>To allow patients who had previously been excluded under the original protocol, an opportunity to be rescreened under the amendment.</p>
<p>2.1</p> <p>5.7.1</p>	<p>Trial Design</p> <p>Follow-up for Subjects Who Discontinue Blinded Study Drug</p>	<p>Revised text to state that subjects who discontinue study medication without withdrawing consent should be counseled to return to the study site for all scheduled safety and efficacy evaluations.</p>	<p>To make consistent with the approach indicated by some health agencies (including the US FDA) that diabetes studies attempt to obtain results from protocol-specified procedures in patients who discontinue study medication (if they agree to remain in the study off of study medication).</p>

**ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:**

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.1.3	Exclusion Criteria	Criteria #22: Clarified the conditions which would, in the judgment of the investigator, make the subject inappropriate for entry into the trial. Criteria #37: Removed text regarding thyroid replacement therapy	Wording clarified and simplified without changing intent of criterion.  Patient must be on a stable dose of thyroid replacement therapy 6 weeks prior to Visit 1/Screening, not Visit 3/Randomization (Day 1)
5.2.1.2.1	Dose Modification of Sitagliptin/Matching Placebo to Sitagliptin	Updated text regarding adverse events which would necessitate interruption or discontinuation of study medication.	To make consistent with updates to the sitagliptin labeling.
5.2.1.2.2	Dose Modification of Dapagliflozin/Matching Placebo to Dapagliflozin	Updated text regarding adverse events which would necessitate interruption or discontinuation of study medication.	To make consistent with updates to the dapagliflozin labeling.
5.5 6.0	Concomitant Medications/Vaccinations (Allowed & Prohibited)  Trial Flow Chart	Added details regarding the requirements for concomitant medication assessments. Added row specifying the review of any prohibited medications, including AHAs other than the trial treatments. Added footnote (f) to clarify the requirements for concomitant medication assessments.	To clarify requirements and ensure patient adherence to protocol. Added row and footnote in trial flow chart to emphasize the importance of reviewing this information

6.0	Trial Flow Chart	<p>Discontinuation Column:                  Updated text to indicate that the Discontinuation Visit is only for subjects who discontinue study medication prematurely.                  Revised footnote (b) to indicate that subjects, who discontinue study medication, should complete procedures for the Discontinuation Visit and (if consent was not withdrawn) continue to be followed by the investigational site, attending scheduled study visits and undergoing study procedures.                  Added footnote (i) to indicate that subjects who are continuing in the study off of double-blind study medication, should not receive study medication and compliance should not be assessed.</p>	<p>To clarify which subjects should have a Discontinuation Visit.                   To clarify which procedures need to be completed by subjects who are continuing in the trial off of study medication.</p>
6.0	Trial Flow Chart	Added "Review of Health Economic Assessment"	Already indicated to be performed (stated study objective); added row in trial flow chart to remind investigators to collect health utilization information.
6.0	Trial Flow Chart	Added footnote (a) to clarify the interval required between Visit 1 and Visit 2.	Footnote added for clarification.



7.2.1	Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor	Added text to define an overdose of dapagliflozin.	In a dose range study of dapagliflozin, the safety and tolerability profile was reported to be generally similar over the dose range studied of 5 to 50 mg per day for 12 weeks in patients with T2DM. Given these results, doses above 50 mg per day (>5 times the dose of dapagliflozin included in this study) will be considered as an overdose.
8.6.1	Statistical Methods for Efficacy Analysis	Removed the analyses that use LOCF to handle missing data. Defined the primary estimands for the study.	To comply with FDA efficacy recommendations.
8.6.2	Statistical Methods for Safety Analysis	Defined the primary and secondary approaches for safety analysis.	To clarify the handling of data collected beyond the 14-day follow-up period after the last dose of blinded study drug.

## 1.0 TRIAL SUMMARY

Abbreviated Title	Sitagliptin vs. Dapagliflozin As Add-on to Metformin With or Without Sulfonyleurea in Subjects with Mild Renal Impairment
Trial Phase	Phase III
Clinical Indication	Treatment of Type 2 Diabetes Mellitus (T2DM)
Trial Type	Interventional
Type of control	Active control
Route of administration	Oral
Trial Blinding	Double-blind
(Select Groups)	Sitagliptin 100 mg q.d., dapagliflozin 10 mg q.d.
Number of trial subjects	Approximately 556 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 75 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 30 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. This will include a 2-week screening period (Visit 1 to Visit 2); a 2-week single-blind placebo run-in period (Visit 2 to Visit 3); a 24-week double-blind, active-comparator-controlled treatment period (Visit 3 to Visit 7); and a post-treatment telephone contact 14 days after the last dose of blinded study drug.
Randomization Ratio	1:1

## 2.0 TRIAL DESIGN

### 2.1 Trial Design

This is a multicenter, randomized, double-blind, active-comparator-controlled, parallel-group clinical trial of sitagliptin in subjects with type 2 diabetes mellitus (T2DM) and mild renal impairment and who have inadequate glycemic control on metformin monotherapy or dual metformin/sulfonyleurea (SU) therapy. This trial will be conducted in conformance with Good Clinical Practices.

The duration of the trial will be up to approximately 30 weeks (with 7 clinic visits) for each subject. This will include a 2-week Screening Period (Visit 1 to Visit 2); a 2-week single-blind placebo run-in period (Visit 2 to Visit 3); a 24-week double-blind, active-comparator-controlled treatment period (Visit 3 to Visit 7); and a post-treatment telephone contact 14 days after the last dose of blinded study drug.

Approximately 556 men and women  $\geq 25$  years of age with T2DM, diagnosed in accordance with American Diabetes Association (ADA) guidelines [1] with inadequate glycemic control (hemoglobin A1c [A1C]  $\geq 7.0\%$  and  $\leq 9.5\%$  [ $\geq 53$  mmol/mol and  $\leq 80$  mmol/mol]) while on a stable dose of metformin ( $\geq 1500$  mg/day for  $\geq 8$  weeks) alone or in dual combination with an SU (at a dose of  $\geq 50\%$  of maximum labeled dose) with an estimated glomerular filtration rate (eGFR)  $\geq 60$  and  $< 90$  mL/min/1.73m<sup>2</sup> as calculated by the CKD-epi equation, and who meet all other enrollment criteria will be randomized.

All subjects will undergo a mixed meal tolerance test (MMTT) at Visit 3/Randomization, before their first dose of double-blind study drug, and at the end of the double-blind treatment period (Visit 7/Week 24 or Discontinuation Visit). At the majority of investigator sites, all subjects will undergo a 2-point, 2-hour MMTT. At selected investigator sites, all subjects will instead undergo a 2-hour, 3-point MMTT. It is expected that approximately 316 subjects will undergo a 2-point, 2-hour MMTT at both time points and approximately 240 subjects will undergo a 3-point, 2-hour MMTT at both time points.

Management of Subjects Prior to Randomization

Subjects on a stable dose of metformin ( $\geq 1500$  mg/day for  $\geq 8$  weeks) in monotherapy or in dual combination with an SU agent (at a dose of  $\geq 50\%$  of maximum labeled dose) with an A1C  $\geq 7.0\%$  and  $\leq 9.5\%$  ( $\geq 53$  mmol/mol and  $\leq 80$  mmol/mol) at Visit 1/Screening, an eGFR  $\geq 60$  and  $< 90$  mL/min/1.73m<sup>2</sup> at Visit 1/Screening and Visit 2/Week -2, and who meet all other enrollment criteria will be eligible to enter the double-blind treatment period beginning at Visit 3/Randomization (Day 1), after completing the 2-week single-blind placebo run-in period (Visit 2/Week -2 to Visit 3/Randomization [Day 1]).

Management of Randomized Subjects

At Visit 3/Randomization (Day 1), subjects will enter the 24-week, double-blind, active-comparator-controlled treatment period and be randomized in a 1:1 ratio to sitagliptin 100 mg once-daily (q.d.) or dapagliflozin once daily. Dapagliflozin/matching placebo will be initiated at 5 mg and titrated up to 10 mg at Visit 4/Week 4. If, in the opinion of the investigator, a subject is unable to tolerate up-titration to 10 mg at Visit 4/Week 4, the subject may remain on dapagliflozin 5 mg/matching placebo; in this case the investigator should continue to assess at subsequent visits whether the subject may be up-titrated to dapagliflozin 10 mg/matching placebo. Dapagliflozin 10 mg/matching placebo may be down-titrated to dapagliflozin 5 mg/matching placebo if subjects demonstrate an inability to tolerate the higher dose. Subjects are to remain on their stable doses of metformin and, for subjects entering on metformin and SU dual combination, stable doses of their SU agent, 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, and remain in the study, off of blinded study medication. These subjects should complete procedures for the Discontinuation Visit at the time they discontinue blinded study therapy, and should then be counseled to return to the study site for all scheduled safety and efficacy evaluations (per Trial Flowchart, see Section 6.0). If a subject is not willing to return to the investigational site for subsequent scheduled study visits, alternative efforts should be made to collect safety and efficacy information, as summarized in Sections 5.7.1 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.

This trial is designed to evaluate, in adult subjects with T2DM and chronic mild renal impairment and who have inadequate glycemic control on diet and exercise and metformin, alone or in dual combination with an SU, the glycemic efficacy, safety, and tolerability of the addition of treatment with sitagliptin over a 24-week treatment period in comparison to the addition of treatment with dapagliflozin.

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](#).

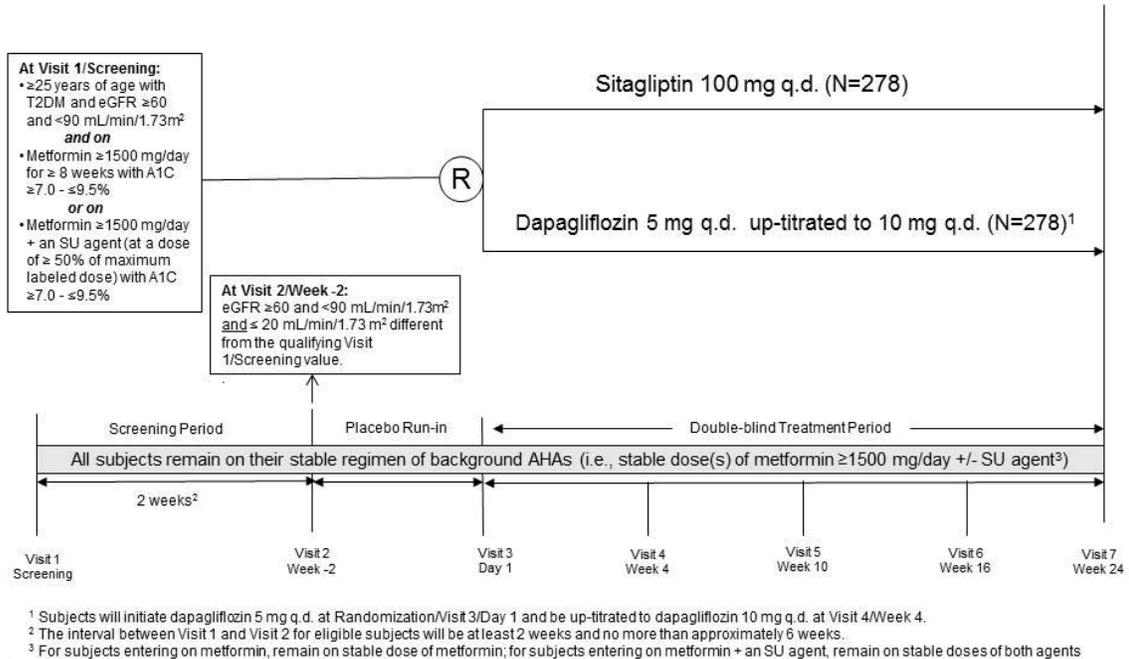


Figure 1 Trial Design

### 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

#### 3.1 Primary Objective(s) & Hypothesis(es)

*In subjects with T2DM and mild renal impairment with inadequate glycemic control on metformin alone or in dual combination with an SU agent:*

- 1) **Objective:** After 24 weeks, to assess the effect of the addition of sitagliptin compared with the addition of dapagliflozin on A1C.

**Hypothesis:** After 24 weeks, the change from baseline in A1C in subjects treated with the addition of sitagliptin is non-inferior compared to that in subjects treated with the addition of dapagliflozin.

**Note:** The non-inferiority margin is 0.3%. The criterion for determining non-inferiority can be found in Section 8 (Statistical Analysis Plan).

- 2) **Objective:** Over 24 weeks, to assess the overall safety and tolerability of sitagliptin in comparison to that of dapagliflozin.

#### 3.2 Secondary Objective(s) & Hypothesis(es)

*In subjects with T2DM and mild renal impairment with inadequate glycemic control on metformin alone or in dual combination with an SU agent, after 24 weeks:*

- 1) **Objective:** To assess the effect of the addition of sitagliptin compared with the addition of dapagliflozin on change from baseline in 2-hour incremental post-prandial glucose excursion.

**Hypothesis:** The addition of sitagliptin provides greater reduction in incremental post-prandial glucose excursion compared with the addition of dapagliflozin.

- 2) **Objective:** To assess the effect of the addition of sitagliptin compared with the addition of dapagliflozin on change from baseline in 2-hour post-prandial glucose (PPG).
- 3) **Objective:** To assess, in a subset of subjects, the effect of the addition of sitagliptin compared with the addition of dapagliflozin on change from baseline in post-prandial insulin AUC, glucagon AUC, and insulin AUC:glucagon AUC ratio.
- 4) **Objective:** To assess the effect of the addition of sitagliptin compared with the addition of dapagliflozin on the proportion of subjects at the A1C goal of <7.0% (<53 mmol/mol).
- 5) **Objective:** To describe the effect of the addition of sitagliptin compared with the addition of dapagliflozin on change in fasting plasma glucose (FPG) from baseline.

#### 3.3 Other Objectives

Over 26 weeks (the 24-week treatment period plus the 2-week safety follow-up period), to assess the effect of the addition of sitagliptin compared with the addition of dapagliflozin on medical resource utilization (e.g., visits to healthcare providers).

## **4.0 BACKGROUND & RATIONALE**

### **4.1 Background**

Refer to the approved labeling for detailed background information on sitagliptin and dapagliflozin.

#### **4.1.1 Pharmaceutical and Therapeutic Background**

There has been a steady increase in the global prevalence of T2DM, largely attributed to rising rates of excess body weight and obesity. In 2011, diabetes was estimated to affect more than 365 million people worldwide between the ages of 20-79 years, and the prevalence of diabetes is projected to reach more than 550 million by the year 2030 [2]. T2DM also represents one of the largest medical burdens in the United States, resulting in direct medical costs of \$176 billion and \$69 billion in loss of productivity in 2012 [3]. At present, it is estimated that 25.8 million people in the US have diabetes (8.3% of the population), of which 7 million remain undiagnosed [4]. T2DM accounts for approximately 90-95% of all cases of diabetes. Individuals with T2DM have an increased risk of developing both microvascular and macrovascular complications, including nephropathy, neuropathy, retinopathy, and cardiovascular disease, and are 2 to 4 times more likely to die from cardiovascular disease than adults who do not have diabetes [5].

In recent years, diabetes experts have reached a consensus that glycemic targets and glucose-lowering therapies should be individualized [6]. Important comorbidities and adverse effects of anti-hyperglycemic agents (AHAs) are among the subject factors that should be considered. Diet, exercise, and education remain the foundation of treatment for T2DM, but most patients will eventually require AHA therapy. Hence, it is essential to understand the relative efficacy and safety/tolerability of available AHA therapies.

Sitagliptin (Merck, Sharp, & Dohme Corp.) is an orally active and highly-selective dipeptidyl peptidase IV (DPP-4) inhibitor indicated for the treatment of patients with T2DM. The therapeutic improvements in glycemic control associated with sitagliptin are mediated by increases in the active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which result from inhibition (by sitagliptin) of the DPP-4 enzyme responsible for inactivation of these peptide hormones. GLP-1 and GIP are released by enteroendocrine L- and K-cells respectively in response to a meal, and result in enhanced glucose-dependent insulin secretion from pancreatic  $\beta$ -cells. In addition, GLP-1 suppresses glucagon release from pancreatic  $\alpha$ -cells and slows gastric emptying. These effects work in concert to lower both fasting and post-prandial glucose concentrations. Clinical studies have shown that sitagliptin (as monotherapy and in combination with other AHAs) is generally well-tolerated, effectively reducing blood glucose concentrations in patients with T2DM. In the United States, sitagliptin (JANUVIA™) is approved as an adjunct to diet and exercise to improve glycemic control as monotherapy and as combination therapy with other AHAs including insulin. In the European Union (EU), sitagliptin (JANUVIA™, TESAVEL™, XELEVIA™) is approved as a restricted first-line oral AHA in patients who cannot tolerate metformin or with contraindication to metformin use. In addition, sitagliptin is approved in the EU as add-on therapy in combination with other AHAs including insulin.

Dapagliflozin (AstraZeneca LP) is an orally active and highly-selective sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated for the treatment of patients with T2DM. Inhibition of the SGLT2 transporter in the proximal tubule of the nephron results in glucose excretion and improved glycemic control. Effects secondary to the glucosuria are an osmotic diuresis resulting in blood pressure reduction and calorie loss resulting in weight loss. Clinical studies have shown that dapagliflozin (as monotherapy and in combination with other AHAs) is generally well tolerated, effectively reducing blood glucose concentrations in patients with T2DM and an eGFR  $\geq 60$  mL/min/1.73m<sup>2</sup>. In the United States, dapagliflozin (FARXIGA™) is approved as an adjunct to diet and exercise to improve glycemic control as monotherapy and as combination therapy with other AHAs including insulin. In the EU, dapagliflozin (FORXIGA™) is approved as a restricted first-line oral AHA in patients who cannot tolerate metformin or with contraindication to metformin use. In addition, dapagliflozin is approved in the EU as add-on therapy in combination with other AHAs including insulin.

## **4.2 Rationale**

### **4.2.1 Rationale for the Trial and Selected Subject Population**

T2DM is a progressive disease, with pancreatic  $\beta$ -cell function declining with increasing duration of the disease. Though initiation of metformin therapy continues to be the standard first-line pharmacologic intervention for the management of hyperglycemia due to T2DM, additional therapies are eventually required to achieve and maintain recommended levels of glycemic control (i.e., A1C <7% for most patients), including addition of an SU agent or a DPP-4 inhibitor, or an SGLT2 inhibitor. Sitagliptin is a DPP-4 inhibitor and is commonly used as add-on to metformin or add-on to metformin/SU to improve glycemic control. Dapagliflozin is a member of a recently approved class of anti-hyperglycemic agents (AHAs) called SGLT2 inhibitors, which is often used as add-on to metformin or add-on to metformin/SU to improve glycemic control. Because the mechanism of action of SGLT2-inhibitors is via the kidney, this class of compounds has less glycemic efficacy in renal impairment and restricted indications for use in patients with moderate and severe renal impairment. Some reduction in efficacy in subjects with only mild renal impairment (eGFR 60 to <90 mL/min/1.73m<sup>2</sup>) has been demonstrated with dapagliflozin as well as other approved compounds in this class [7, 8] but prospectively designed studies comparing efficacy, safety and tolerability of this class to other AHAs in subjects with mild renal impairment have not been done. Moreover, though sitagliptin clinical trials have included subjects who meet eGFR criteria for mild renal impairment, this sub-group has not been specifically studied in a dedicated clinical trial of sitagliptin.

Renal impairment is common in patients with T2DM, and 38% of individuals with T2DM are estimated to have chronic mild renal impairment [9]. Minimum age for inclusion in this trial is 25 years old, in order to provide added assurance that the mild renal impairment is due to an underlying chronic condition (e.g., T2DM) rather than due to a primary renal disease which may progress rapidly. This study will evaluate the relative glycemic efficacy (by assessment of non-inferiority of A1C reduction) and the relative safety/tolerability profile of sitagliptin in comparison to dapagliflozin in subjects with T2DM and mild renal impairment who have inadequate glycemic control on a background of metformin alone or dual combination with an SU in conjunction with diet and exercise.

#### **4.2.2 Rationale for Dose Selection/Regimen**

##### **4.2.2.1 Rationale for Sitagliptin Dose**

The approved dose for patients with creatinine clearance (CrCl)  $\geq 50$  mL/min is sitagliptin 100 mg once daily. Given that this study will enroll subjects with mildly impaired renal function (eGFR 60 to  $<90$  mL/min/ $1.73\text{m}^2$ ), sitagliptin 100 mg once daily is appropriate.

##### **4.2.2.2 Rationale for Dapagliflozin Dose**

The recommended dose of dapagliflozin is 10 mg once daily. In accordance with the US labeling, the starting dose in this trial will be 5 mg once daily. At Visit 4/Week 4 of the treatment period, dapagliflozin will be up-titrated to 10 mg daily in all subjects unless, in the opinion of the investigator, the subject is unlikely to tolerate the 10 mg dose. Subjects on the 10 mg dose who, in the opinion of the investigator, are unable to tolerate the 10 mg dose may be down-titrated to the 5 mg dose.

#### **4.2.3 Rationale for Endpoints**

##### **4.2.3.1 Efficacy Endpoints**

Glycemic efficacy endpoints will be A1C, FPG, 2-hour post-prandial glucose (PPG), 2-hour incremental post-prandial glucose excursion, and post-prandial insulin, glucagon, and insulin:glucagon ratio. A1C reflects average glucose concentrations in the past 3-4 months and, therefore, provides a useful index of the glycemic control of sitagliptin and dapagliflozin over that time period. It is a standard efficacy endpoint used to assess the glycemic efficacy of AHAs, and improvement in A1C correlates with reduction of risk of diabetic complications. Although sitagliptin lowers both the post-prandial rise in glucose and fasting glucose levels, a greater effect on the incremental post-prandial glucose is usually observed [10]. Some studies have highlighted the role of post-prandial glucose excursions in contributing to diabetic complications, and suggested the importance of post-meal glucose control [11]. Assessment of incremental post-prandial glucose excursion will provide insight into the relative effects of sitagliptin and dapagliflozin on post-prandial glucose control, with 2-hr PPG evaluating both post-meal and fasting control. Assessment of post-prandial insulin, glucagon, and insulin:glucagon will aid in understanding of the relative effects of sitagliptin and dapagliflozin on hormonal regulation of glucose. Assessment of FPG will characterize the earlier time course of glucose control in this trial.

Although subjects randomized to dapagliflozin will be on maximum dose for 20 weeks (due to the up-titration at Visit 4/Week 4 of the double-blind treatment period) while subjects randomized to sitagliptin will be on maximum dose for 24 weeks, this should not bias the efficacy assessment in favor of sitagliptin, since both dapagliflozin and sitagliptin are expected to achieve maximal glycemic efficacy by 18 weeks of treatment. Therefore, the protocol design allows a valid comparison of efficacy between the two treatments.

#### **4.2.3.2 Safety Endpoints**

Safety assessment will include collection of adverse events (AEs), a hypoglycemia assessment log to collect information on each potential episode (including concurrent fingerstick glucose value), physical examination including vital signs and postural blood pressure/heart rate. Laboratory safety studies will include blood chemistry, lipid panel, hematology, and urine pregnancy testing (performed in women of childbearing potential). Refer to Section 8.0 for further details.

#### **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. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

### **4.3 Benefit/Risk**

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the Informed Consent documents.

## 5.0 METHODOLOGY

### 5.1 Entry Criteria

#### 5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with T2DM and mild renal impairment on metformin alone or in combination with an SU agent and who are at least 25 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 in accordance with ADA guidelines [1] and be  $\geq 25$  years of age on the day of signing the ICF.
2. Have an eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> and  $< 90$  mL/min/1.73 m<sup>2</sup>, as calculated by the CKD-epi equation [12].

**Note:** Subjects with eGFR not meeting this criterion, but with an eGFR value within 5 mL/min/1.73 m<sup>2</sup> of this range (i.e.,  $\geq 55$  and  $\leq 95$  mL/min/1.73 m<sup>2</sup>), may have a single repeat value, and continue in the study if the repeat value meets the inclusion criterion.

3. Be on metformin  $\geq 1500$  mg/day alone or in combination with an SU agent (at a dose of  $\geq 50\%$  maximum labeled dose in the country of the investigational site) for  $\geq 8$  weeks with a Visit 1/Screening A1C  $\geq 7.0\%$  and  $\leq 9.5\%$  ( $\geq 53$  mmol/mol and  $\leq 80$  mmol/mol).
4. Have a body mass index (BMI)  $\geq 18.0$  kg/m<sup>2</sup>.
5. Have personally signed and dated the ICF indicating that he/she has been informed of all pertinent aspects of the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
6. Be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
7. Meet one of the following criteria:
  - a. Subject is a male.
  - b. Subject is a female not of reproductive potential defined as one who:
    - 1) Is postmenopausal (defined as at least 12 months with no menses in women  $\geq 45$  years of age), or

- 2) Has had a hysterectomy and/or bilateral oophorectomy, or had bilateral tubal ligation or occlusion at least 6 weeks prior to Visit 1/Screening.
- c. Subject is a female of reproductive potential and:
- 1) agrees to remain abstinent from heterosexual activity (if this form of birth control is accepted by local regulatory agencies and ethics review committees as the sole method of birth control for subjects participating in clinical trials), or
  - 2) agrees to use (or have her partner use) acceptable contraception to prevent pregnancy while receiving blinded study drug and for 14 days after the last dose of blinded study drug. Two methods of contraception will be used to avoid pregnancy. Acceptable combinations of methods include:
    - Use of one of the following double-barrier methods: diaphragm with spermicide and a condom; cervical cap and a condom; or a contraceptive sponge and condom.
    - Use of hormonal contraception (any registered and marketed contraceptive agent that contains and estrogen and/or a progestational agent [including oral, subcutaneous, intrauterine and intramuscular agents, and cutaneous patch]) with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom, vasectomy, or IUD.
    - Use of an IUD with one of the following: condom; diaphragm with spermicide; contraceptive sponge; vasectomy; or hormonal contraception (see above).
    - Vasectomy with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; IUD; or hormonal contraception (see above).

**At Visit 2/Week -2**

8. Have an eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> and  $< 90$  mL/min/1.73 m<sup>2</sup>, as calculated by the CKD-epi equation and  $\leq 20$  mL/min/1.73 m<sup>2</sup> different from the qualifying Visit 1/Screening value.

**Note (1):** The Visit 1 and Visit 2 eGFR measurements must be at least 2 weeks apart and should be no more than 6 weeks apart.

**Note (2):** If the above eGFR criteria is not met, but the eGFR value is  $\leq 30$  mL/min/1.73 m<sup>2</sup> different than the qualifying Visit 1 eGFR value, a single repeat may be performed, and the subject is eligible if the repeat meets the above eGFR inclusion criterion.

**At Visit 3/Randomization/Day 1**

9. Be  $\geq 80\%$  compliant with placebo run-in medication (as determined by site-performed pill count).

**5.1.3 Subject Exclusion Criteria**

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

**At Visit 1/Screening**

**Diabetes Diagnosis and Prior Therapy Criteria**

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

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

2. Has a history of secondary causes of diabetes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant).
3. Has a known hypersensitivity or intolerance to any DPP-4 inhibitor or SGLT2 inhibitor.
4. Has been treated with any of the following agents within 12 weeks of **Visit 1/Screening**:
  - Insulin of any type (except for short-term use [i.e.,  $\leq 7$  days] during concomitant illness or other stress)
  - DPP-4 inhibitors
  - Pioglitazone or rosiglitazone
  - GLP-1 agonists
  - SGLT2 inhibitors
  - Alpha glucosidase inhibitors
  - Meglitinides
  - Bromocriptine
  - Colesevelam
  - Any other AHA with the exception of metformin and for subjects on dual combination therapy, a sulfonylurea
5. Subject intends to initiate weight loss medication during the study period.
6. Subject has undergone bariatric surgery within 12 months of Visit 1/Screening.

7. Subject is not weight stable (defined as  $\geq 5\%$  change in body weight in the last 6 months; this may be per subject report).
8. Subject has started a weight loss medication (such as orlistat, phentermine, or sibutramine) or a medication associated with weight changes (e.g., anti-psychotic medications) within the prior 12 weeks.

**Concomitant Disease of Organs and Systems**

9. Has a history of myocardial infarction, unstable angina, arterial revascularization, stroke, transient ischemic attack, or NYHA functional class III-IV heart failure within 3 months of Visit 1/Screening.
10. Is at high risk for volume depletion, hypotension and/or electrolyte imbalances, in the opinion of the investigator.
11. Has a history of malignancy  $\leq 5$  years prior to signing the ICF, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer:  
**Note (1):** A subject with a history of malignancy  $>5$  years prior to signing the ICF should have no evidence of residual or recurrent disease.  
**Note (2):** A subject with any history of melanoma, leukemia, lymphoma, bladder cancer, or renal cell carcinoma is excluded.
12. Has human immunodeficiency virus (HIV) as assessed by medical history.
13. Has
  - Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells, or
  - Clinically important hematological disorder (such as aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia).
14. Has a medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic hepatitis B or C (assessed by medical history), primary biliary cirrhosis, or symptomatic gallbladder disease.
15. Has any clinically significant malabsorption condition.
16. Is currently being treated for hyperthyroidism.
17. Is on thyroid replacement therapy and has not been on a stable dose for at least 6 weeks prior to Visit 1/Screening.  
**Note:** Subjects who meet this criterion may be re-screened after being on a stable dose of thyroid replacement therapy for at least 6 weeks.
18. Is on or likely to require treatment for  $\geq 14$  consecutive days or repeated courses of pharmacologic doses of corticosteroids.  
**Note:** Inhaled, nasal, ophthalmic, and topical corticosteroids and physiological replacement doses of adrenal steroids are permitted.

19. Is on or likely to require treatment for  $\geq 7$  consecutive days with non-steroidal anti-inflammatory drugs.

**Note:** Does not apply to chronic aspirin (ASA) therapy ( $\leq 325$  mg daily).

20. Has undergone a surgical procedure within 12 weeks prior to signing the ICF or has major surgery planned during the trial.

**Note:** A subject who has undergone minor surgery within the 12 weeks prior to Visit 1/Screening and is fully recovered or a subject who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia.

21. Has a mean value for duplicate sitting systolic blood pressure  $>160$  mm Hg and/or diastolic blood pressure  $>90$  mm Hg (after at least a 5-minute seated rest) and blood pressure is considered unlikely to be below these limits by Visit 3/Randomization (Day 1) with initiation or adjustment of antihypertensive medication.

**Note:** Investigators are encouraged to maximize blood pressure control according to current guidelines. The subject may have blood pressure medication initiated or adjusted and be enrolled if repeat blood pressure measurements no longer meet the exclusion criterion at Visit 3/Randomization (Day 1). Subjects on blood pressure medication must be on a stable regimen for at least 4 weeks prior to Visit 3/Randomization (Day 1).

22. Has other medical condition, psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial.

**Exclusion Criteria Based on Laboratory Abnormalities**

23. Has an exclusionary laboratory value as listed in [Table 1](#) below:

Table 1 Laboratory Exclusion Criteria

Parameter <sup>1</sup>	Population (if applicable)	Trial Limit for Exclusion
Alanine aminotransferase (ALT)		$>2$ times Upper Limit of Normal (ULN)
Aspartate aminotransferase (AST)		$>2$ times ULN
Thyroid-stimulating hormone (TSH) <sup>2</sup>		Outside central laboratory normal range
Hemoglobin	Male Female	$<12$ g/dL (120 g/L) $<11$ g/dL (110 g/L)
Triglycerides (TG) <sup>3</sup>		$>600$ mg/dL (6.78 mmol/L)

<sup>1</sup> 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 laboratory test not meeting entry criterion should be repeated (not the entire panel). The last laboratory draw/result should be used for inclusion.

<sup>2</sup> Subjects excluded due to the TSH criterion may be re-screened after being on a stable thyroid replacement therapy for at least 6 weeks.

<sup>3</sup> Subjects with elevated TG levels may have lipid-lowering medication initiated or adjusted and continue in the trial if a repeat measurement (at Visit 2/Week -2) no longer meets the exclusion criterion. Subjects on lipid-lowering medication must be on a stable regimen for at least 4 weeks prior to Visit 3/Randomization (Day 1).

### Other Criteria

24. Has participated in other studies involving investigational drug(s) (Phase I-IV) within 30 days prior to Visit 1/Screening or during the pre-randomization period.
25. Has a positive urine pregnancy test.
26. Is pregnant or breast-feeding, or is planning to conceive during the trial, including 14 days following the last dose of blinded study drug.
27. Is planning to undergo hormonal therapy in preparation to donate eggs during the trial, including 14 days following the last dose of blinded study drug.
28. Routinely consumes >2 alcoholic drinks per day or >14 alcoholic drinks per week or engages in binge drinking.  
**Note (1):** One alcoholic drink is defined as 5 oz. (150 mL) of wine, or 12 oz. (350 mL) of beer, or 1.5 oz. (50 mL) of 80-proof liquor.  
**Note (2):** Binge drinking is defined as a pattern of 5 or more alcoholic drinks (male), or 4 or more alcoholic drinks (female) in about 2 hours.
29. Has donated blood or blood products within 6 weeks of Visit 1/Screening or who plans to donate blood or blood products at any time during the trial.
30. 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 2/Week -2

31. Has a clinically significant ECG abnormality that requires further diagnostic evaluation or intervention (e.g., new, clinically significant arrhythmia or a conduction disturbance).
32. Has a FPG consistently (i.e., measurement repeated and confirmed within 7 days) >260 mg/dL (14.4 mmol/L).
33. Has a positive urine pregnancy test.
34. Has a fasting TG level >600 mg/dL (6.8 mmol/L).

**Note:** This criterion applies to subjects who met the exclusion criterion for TG levels at Visit 1/Screening and who required evaluation of TG levels at Visit 2/Week -2 to assess eligibility following initiation or adjustment of lipid-lowering medication.

### At Visit 3/Randomization (Day 1)

35. Has a site fasting fingerstick glucose (FFSG) <110 mg/dL (6.1 mmol/L) or >260 mg/dL (14.4 mmol/L).

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

If the subject meets this FFSG exclusion criterion at the rescheduled Visit 3/Randomization (Day 1), the subject MUST be excluded.

36. Has a positive urine pregnancy test.
37. Is on lipid-lowering medication or blood pressure medication and *has not* been on a stable regimen for the 4 weeks prior to Visit 3/Randomization (Day 1).

Note: The current visit can be changed to an Unscheduled Visit, and the subject should be rescheduled for a Visit 3/Randomization (Day 1). Additional single-blind placebo run-in medication should be dispensed if needed.

38. Has a mean value for duplicate sitting systolic blood pressure of >160 mm Hg and/or diastolic blood pressure of >90 mm Hg (after at least a 5-minute seated rest).
39. Has developed a new medical condition, suffered a change in status of an established medical condition, developed a laboratory or ECG abnormality, or required a new treatment of medication during the pre-randomization period which meets any previously described trial exclusion criteria or which, in the opinion of the investigator, exposes the subject to risk by enrolling in the trial.

**Note:** Subjects that were excluded based upon eGFR or A1C criteria in Protocol 838-00, but may be eligible under Protocol 838-02 may be rescreened once (returning to the site for a Screening Visit/Visit 1); similarly, subjects on metformin and a sulfonylurea, eligible under Protocol 838-02 may be rescreened once (returning to the site for a Screening Visit/Visit 1); see site Data Entry Guidelines for specific details).

## 5.2 Trial Treatment(s)

Treatments to be used in this trial are outlined below in [Table 2](#).

Table 2 Trial Treatments

Treatment Group	Drug/Dose	Use	Dose Frequency/ Treatment Period	Route of Administration
placebo run-in (all groups)	matching placebo for sitagliptin 100 mg	placebo (trial drug)	q.d. for 2 weeks	oral
	matching placebo for dapagliflozin 5 mg	placebo (active-comparator)		
sitagliptin 100 mg group	sitagliptin 100 mg	investigational (trial drug)	q.d. for 24 weeks	oral
	matching placebo for dapagliflozin 5 mg	placebo (active-comparator)	q.d. for 4 weeks <sup>1</sup>	
	matching placebo for dapagliflozin 10 mg		q.d. for 20 weeks <sup>2</sup>	
dapagliflozin 10 mg group	dapagliflozin 5 mg	active-comparator	q.d. for 4 weeks <sup>1</sup>	oral
	dapagliflozin 10 mg		q.d. for 20 weeks <sup>2</sup>	
	matching placebo for sitagliptin 100 mg	placebo (trial drug)	q.d. for 24 weeks	

<sup>1</sup> Starting at Visit 3/Randomization (Day 1) through one day prior to Visit 4/Week 4.  
<sup>2</sup> Starting at Visit 4/Week 4 and for the duration of the double-blind treatment period. Up-titration to 10 mg q.d./matching placebo may be delayed if subject is unable to tolerate up-titration in the opinion of the investigator. Dapagliflozin 10 mg q.d./matching placebo may be down-titrated to dapagliflozin 5 mg q.d. if subject is unable to tolerate the higher dose in the opinion of the investigator.

The first doses of single-blind matching placebo for sitagliptin and matching placebo for dapagliflozin will be administered at the trial site as witnessed doses at Visit 2/Week -2.

The first doses of double-blind sitagliptin/matching placebo and dapagliflozin/matching placebo will be administered at the trial site as witnessed doses at Visit 3/Randomization (Day 1), after completion of study procedures including MMTT. Subsequent dosing will be performed once-daily by the subject unsupervised at his/her home at approximately the same time each day in the morning.

Supply of background metformin (and SU, for subjects on an SU) will be the responsibility of the subject throughout the duration of the trial.

Sitagliptin 100 mg and matching placebo will be administered in a blinded manner as oral tablets q.d. Dapagliflozin 5 mg, dapagliflozin 10 mg, and matching placebos will be administered in a blinded manner as oral capsules q.d. Hence, **all subjects will take 1 tablet and 1 capsule each day**.

Subjects randomized to sitagliptin 100 mg q.d. will take one sitagliptin 100 mg tablet and one matching placebo capsule for dapagliflozin 5 mg daily starting at Visit 3/Randomization (Day 1) through one day prior to Visit 4/Week 4. Starting at Visit 4/Week 4, and for the duration of the double-blind treatment period, subjects will then take one sitagliptin 100 mg tablet and one matching placebo capsule for dapagliflozin 10 mg daily.

Subjects randomized to dapagliflozin 10 mg q.d. will take one dapagliflozin 5 mg capsule and one matching placebo tablet for sitagliptin 100 mg daily starting at Visit 3/Randomization (Day 1) through one day prior to Visit 4/Week 4. Starting at Visit 4/Week 4, and for the duration of the double-blind treatment period, subjects will then take one dapagliflozin 10 mg capsule and one matching placebo tablet for sitagliptin 100 mg daily.

If a subject is unable to tolerate up-titration of dapagliflozin (or matching placebo) at Visit 4/Week 4 from 5 mg to 10 mg, the subject will continue taking the dapagliflozin 5 mg capsule (or matching placebo). In this case, the investigator may up-titrate the subject at a subsequent study visit if, in the opinion of the investigator, the subject becomes able to tolerate the 10 mg dose. If a subject is up-titrated to the dapagliflozin 10 mg capsule (or matching placebo) but is unable to tolerate this dose, the investigator should down-titrate the subject to the dapagliflozin 5 mg dose (or matching placebo). Any up-titration or down-titration of dapagliflozin dose will be done via IVRS dispensing of new study medication.

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 (Escalation/Titration/Other)**

#### **5.2.1.2.1 Dose Modification of Sitagliptin/Matching Placebo to Sitagliptin**

The dose of sitagliptin or matching placebo cannot be modified throughout the 24-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.

#### **5.2.1.2.2 Dose Modification of Dapagliflozin/Matching Placebo to Dapagliflozin**

The dose of dapagliflozin or matching placebo will be up-titrated at Visit 4/Week 4 from 5 mg q.d. to 10 mg q.d. If, in the opinion of the investigator, a subject is unable to tolerate up-titration at Visit 4/Week 4, the subject may remain on the 5 mg dose; in this case, the investigator should assess at subsequent study visits whether the subject is now likely to tolerate up-titration. For subjects up-titrated to 10 mg, the dose of dapagliflozin or matching placebo cannot be modified unless, in the opinion of the investigator, the subject has demonstrated an inability to tolerate the 10 mg dose of dapagliflozin. In this case, dapagliflozin or matching placebo should be down-titrated to 5 mg q.d.

If a subject is determined to have volume depletion, dapagliflozin (or matching placebo) should be interrupted and reinstated only after volume depletion has been corrected.

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

### **5.2.1.2.3 Dose Modification of Metformin and Sulfonylurea**

The dose of metformin ( $\geq 1500$  mg/day) and, for subjects on metformin and an SU agent, the dose of the SU agent, should remain stable throughout the 24-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 reinstated only after renal function has been evaluated and found not to have been reduced by the dye study.

Subjects on metformin and an SU agent should have the SU agent downtitrated or interrupted, as clinically appropriate, for events of unexplained severe hypoglycemia or recurrent hypoglycemia, and the subject continued in the study (see also Section 5.7 Subject Withdrawal/Discontinuation Criteria).

### **5.2.2 Timing of Dose Administration**

At Visit 3/Randomization/Day 1, each subject will be randomly assigned to sitagliptin 100 mg q.d. or dapagliflozin. At this visit, subjects will take study medication as instructed after the MMTT has been completed (see Section 7.1.2.9 for details).

On days without clinic visits, subjects should take double-blind study drug (sitagliptin, dapagliflozin and matching placebos) orally at approximately the same time of the morning.

Subjects will be instructed not to take double-blind study drug the morning of the clinic visit.

On the days of clinic visits, subjects will take blinded study drug as well as background metformin (and SU, for subjects also on an SU agent) after all study procedures are completed, with the exception of Visit 7/Week 24 (or Discontinuation Visit). At Visit 7/Week 24 (or Discontinuation Visit), subjects will take blinded study drug and background metformin (and SU, for subjects also on an SU agent) as part of the MMTT, approximately 1 hour before consuming the standard meal for the MMTT (see Section 7.1.2.9 for details.)

If a subject misses a dose of blinded study drug 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.

### **5.2.3 Trial Blinding/Masking**

A double-blind/masking technique will be used. Sitagliptin and dapagliflozin will be packaged identically relative to their matching placebos so that the 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**

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 sitagliptin 100 mg q.d. or dapagliflozin.

### **5.4 Stratification**

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

### **5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)**

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

AHAs taken by the subject at any time prior to Visit 1/Screening and any other medications taken within 8 weeks of Visit 1/Screening should be recorded on the appropriate electronic case report form (eCRF). The site may rely on subject report for this information. Concomitant medications taken during the trial must also be recorded.

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

#### **Prohibited Medications**

Medications listed below are prohibited while subjects are receiving blinded investigational product during the double-blind treatment period:

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, sulfonylurea (if applicable), and double blinded study medication during study participation.

1. Other Antihyperglycemic Medications:

- Insulin of any type (except for short-term use [i.e., <7 days] during concomitant illness or other stress)
- GLP-1 agonists
- Pioglitazone or rosiglitazone
- DPP-4 inhibitors (except blinded sitagliptin)
- SGLT2 inhibitors (except blinded dapagliflozin)
- Alpha glucosidase inhibitors
- Meglitinides
- Bromocriptine
- Colesevelam
- Any other AHA with the exception of metformin, and for patients on dual combination therapy, a sulfonylurea, and double-blind study drug

2. Corticosteroids: Treatment for  $\geq 14$  consecutive days or repeated courses of pharmacologic doses of corticosteroid is prohibited.

**Note:** Inhaled, nasal, and topical corticosteroids and physiological replacement doses of adrenal steroids are permitted.

3. Weight-loss Medications: Initiation of a weight-loss medication (e.g., orlistat, phentermine, topiramate, lorcaserin) is prohibited.

**Note:** Subjects who are on treatment with a weight-loss medication or other medication associated with weight changes (e.g., anti-psychotic agents) and who are weight-stable (i.e., <5% change in body weight within 6 months of Visit 1/Screening) at Visit 1/Screening are eligible to participate in the study and permitted to continue these medications during the study. Subjects who require adjustment or initiation of other medications associated with weight changes during the study should be discussed with the Sponsor.

4. Cimetidine: Initiation of cimetidine on a regular or as needed basis is prohibited. If a subject requires an H2 antagonist during the study, an alternate agent should be used.

**Note:** Subjects who are taking regular (at least daily) and consistent cimetidine at Visit1/Screening may continue, but should be instructed not to change the use or dose of cimetidine during the study.

### **Guidance for Other Medications**

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

1. **Blood Pressure and Lipid-altering Medications:** Concurrent blood pressure and lipid-lowering medications are permitted. Subjects should be on stable doses of these medications for at least 4 weeks before Visit 3/Randomization (Day 1) and during the study. Subjects whose blood pressure or lipid-lowering medications are not stable at Visit 1/Screening should be scheduled appropriately to ensure these medications are stable for at least 4 weeks prior to Visit 3/Randomization (Day 1).
2. **Hormonal Replacement Therapy and Birth Control Medications:** Hormone replacement therapy and birth control medications are permitted, but subjects should be on stable regimens, and are expected to remain on their stable regimen while receiving blinded study drug during the double-blind treatment period and for 14 days after the last dose of blinded study drug.
3. **Thyroid Hormone Replacement Therapy:** Thyroid replacement medication (e.g., thyroxine) is permitted, but subjects should be on a stable dose for at least 6 weeks prior to Visit 1/Screening. Subjects who meet the TSH exclusion criterion specified in [Table 1](#) may be re-screened after being on a stable thyroid replacement regimen for at least 6 weeks.
4. **Supplemental and/or Traditional Medicines:** The use of herbal supplements and other natural products should be discouraged. Subjects who do not discontinue the use of such supplements prior to Visit 2/Week -2 should be instructed not to change the use or dose of the supplement during the trial. Subjects should be instructed not to initiate new supplements during the trial.

## **5.6 Diet/Activity/Other Considerations**

### **5.6.1 Diet**

Subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at Visit 2/Week -2; 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.

### 5.6.2 Alcohol, Caffeine and Tobacco

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

### 5.6.3 Activity

Subjects will be counseled to maintain a medically appropriate, routine exercise program and consistent physical activity level during the trial.

Subjects should avoid strenuous exercise for 24 hours prior to the MMTT, performed at Visit 3/Randomization and at Visit 7 (or Discontinuation).

### 5.7 Subject Withdrawal/Discontinuation Criteria

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

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

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

- The subject withdraws consent.

**Note:** Since follow-up health status information is important to the full evaluation of any investigational agent, **the investigator should determine if a subject who no longer agrees to actively participate (i.e., no longer attend visits at the investigational site, take blinded study drug, and have other study-related procedures conducted at the investigational site) is agreeable to providing additional follow-up information through interval telephone contacts** (with the site collecting important health status information [e.g., SAEs]). See Section 5.7.1 for additional details about monitoring subjects who discontinue treatment with blinded 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. Subject meets protocol-specified hyperglycemia criteria, as specified below:

Subjects who have a repeated, confirmed FPG or single A1C value meeting relevant glycemic discontinuation threshold (see below) for the specific time point in the trial, without a reasonable explanation (e.g., intercurrent illness or medication omission) :

- FPG consistently >270 mg/dL (15.0 mmol/L) after Visit 3/Day 1 through Visit 4/Week 4.
- FPG consistently >240 mg/dL (13.3 mmol/L) after Visit 4/Week 4 through Visit 5/Week 10.
- FPG consistently >200 mg/dL (11.1 mmol/L) or A1C >8.0% (64 mmol/mol) after Visit 5/Week 10 through Visit 7/Week 24.

**Note:** A consistent value for FPG is defined as a repeat measurement performed within 7 days of notification from the central laboratory. Site should reinforce diet/exercise counseling prior to repeat measurement.

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

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

Note: for subjects on an SU agent, the SU agent should be interrupted (see Section 5.2.1.2.3) prior to evaluation of the subject for discontinuation due to hypoglycemia.

3. Abnormal liver function tests meeting criteria specified below (see Section 12.5 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 12.5.

4. Reduction of renal function:

- eGFR persistently <50 mL/min/1.73m<sup>2</sup> (CKD-epi formula) from Visit 3/Day 1 through one day prior to Visit 5/Week 10.

**Note:** A persistent value is defined as a repeat measurement, performed 2 to 3 weeks after notification from the central laboratory, that remains  $<50$  mL/min/1.73m<sup>2</sup> despite correction of potential causative factors (e.g., correction of volume depletion, discontinuation of nonsteroidal anti-inflammatory drugs [NSAIDs]). If the eGFR value continues to meet the discontinuation criterion but demonstrates stability or improvement relative to the prior result, an additional repeat may be performed.

- eGFR persistently  $<60$  mL/min/1.73m<sup>2</sup> (CKD-epi formula) from Visit 5/Week 10 through Visit 7/Week 24.

**Note:** A persistent value is defined as a repeat measurement, performed 2 to 3 weeks after notification from the central laboratory, that remains  $<60$  mL/min/1.73m<sup>2</sup> despite correction of potential causative factors (e.g., correction of volume depletion, discontinuation of NSAIDs). If the eGFR value continues to meet the discontinuation criterion but demonstrates improvement relative to the prior result, an additional repeat may be performed.

See Section 7.1.12.5 for guidance on following subjects who discontinue blinded study drug due to decreased renal function or renal-related adverse events.

5. Requirement for one of the prohibited medications listed in Section 5.1.3.
6. Pregnancy.

**Note:** A positive urine pregnancy test requires immediate interruption of blinded study drug until serum  $\beta$ -hCG can be performed and found to be negative. Subject must be permanently discontinued from blinded study drug, and pregnancy should be reported and followed per Section 7.2.2 if pregnancy is confirmed by a positive serum pregnancy test.

7. 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.
8. 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 5.7.1.

## **5.7.1 Follow-up for Subjects Who Discontinue Blinded Study Drug**

### **5.7.1.1 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 withdraw consent, the subject should be encouraged to complete procedures for the Discontinuation Visit (when they discontinue blinded study therapy, and withdraw consent).

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

### **5.7.1.2 Discontinuation from Blinded Study Therapy**

A subject who discontinues treatment with blinded study drugs for reasons other than withdrawn consent *or* a subject for whom the investigator recommends discontinuation of study medication should complete a Discontinuation Visit, and have a post-treatment telephone call approximately 14 days after the last dose of blinded study medication. 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 subject should then be counseled to return to the study site for all scheduled safety and efficacy visits, completing all trial procedures (other than procedures related to study medication, or the MMTT), as indicated in the Trial Flowchart (Section 6.0).

If the subject who has discontinued study medications is unwilling to return for scheduled study visits, alternative efforts should be made to collect safety and efficacy information; this may include more limited study visits and/or telephone contacts (to collect information about the subject's health status, including collection of any SAEs) according to the study schedule until the end of the trial (Week 24).

Subjects who discontinue treatment with blinded study drugs but who continue to participate in the trial by providing follow-up information can receive medical and diabetes management by their managing physician or investigator, as appropriate. These subjects may initiate any other therapy as needed (previously prohibited medications will not apply to them). Procurement of other AHAs, including background AHA, 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.

## **5.8 Subject Replacement Strategy**

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

## **5.9 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).

## **5.10 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	Run-In	Randomization	Double-Blind Treatment				Post-Treatment	
Visit Number	1	2 <sup>a</sup>	3	4	5	6	7	Early Discontinuation	Follow-up
Scheduled Week		-2	0 (Day 1)	4	10	16	24	At time of Discontinuation of study medication <sup>b</sup>	14-Day Post Treatment Telephone Contact <sup>c</sup>
Visit Window Guideline (days)		±5	±5	±7	±7	±7	±7		
<b>Administrative Procedures</b>									
Informed Consent <sup>d</sup>	X								
Informed Consent for Future Biomedical Research <sup>e</sup>	X								
Assignment of Screening Number	X								
Contact IVRS	X	X	X	X	X	X	X	X	
Subject Identification Card	X								
Assignment of Randomization Number			X						
<b>Trial Compliance</b>									
Inclusion/Exclusion Criteria	X	X	X						
Prior/Concomitant Medication Review <sup>f</sup>	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 <sup>f</sup>	X	X	X	X	X	X	X	X	
Diet and Activity Counseling/Monitoring <sup>g</sup>		X	X	X	X	X	X	X	
Dispense Hypoglycemia Assessment Log (HAL) and Instruct on Hypoglycemia Symptoms and Management		X							
Dispense Glucose Meter and Provide SMBG Instruction		X							
<b>Study Drug</b>									
Dispense Single-Blind Placebo Run-In		X							
Witness Dose of Blinded Study Drug in Clinic <sup>h</sup>		X	X						

Trial Period:	Screening	Run-In	Randomization	Double-Blind Treatment				Post-Treatment	
Visit Number	1	2 <sup>a</sup>	3	4	5	6	7	Early Discontinuation	Follow-up
Scheduled Week		-2	0 (Day 1)	4	10	16	24	At time of Discontinuation of study medication <sup>b</sup>	14-Day Post Treatment Telephone Contact <sup>c</sup>
Visit Window Guideline (days)		±5	±5	±7	±7	±7	±7		
Dispense Double-Blind Study Drug <sup>h</sup>			X	X	X	X			
Assess Compliance with Blinded Study Drug <sup>i</sup>			X	X	X	X	X	X	
<b>Clinical Procedures/Assessments</b>									
Demographics and Medical History	X								
Height	X								
Weight	X		X		X		X	X	
Vital Signs (Pulse Rate and Blood pressure)	X	X	X	X	X	X	X	X	
Postural (Orthostatic) Blood Pressure/Pulse Rate			X	X	X	X	X	X	
Full Physical Exam <sup>l</sup>		X							
Brief Physical Exam <sup>k</sup>							X	X	
12-Lead ECG <sup>l</sup>		X							
Site Fingerstick A1C Measurement <sup>m</sup>	X								
Fasting Fingerstick Glucose in Clinic			X						
Review of SMBG Measurements and HAL			X	X	X	X	X	X	
Adverse Events Monitoring		X	X	X	X	X	X	X	X
Health Economic Assessment		X	X	X	X	X	X	X	
<b>Laboratory Procedures/Assessments</b>									
FPG	X	X	X	X	X	X	X	X	
A1C <sup>n</sup>	X		X		X	X	X	X	
Fasting C-peptide	X <sup>o</sup>								
Lipid Panel <sup>p</sup>			X				X	X	
Chemistry Panel	X	X	X	X	X	X	X	X	
Hematology	X		X		X		X	X	

Trial Period:	Screening	Run-In	Randomization	Double-Blind Treatment				Post-Treatment	
Visit Number	1	2 <sup>a</sup>	3	4	5	6	7	Early Discontinuation	Follow-up
Scheduled Week		-2	0 (Day 1)	4	10	16	24	At time of Discontinuation of study medication <sup>b</sup>	14-Day Post Treatment Telephone Contact <sup>c</sup>
Visit Window Guideline (days)		±5	±5	±7	±7	±7	±7		
Fasting Triglycerides	X	X <sup>q</sup>							
TSH	X								
Urine Pregnancy Test (Women of childbearing potential only <sup>f</sup> )	X	X	X	X	X	X	X	X	
2 point- MMTT at selected sites: Blood samples at 0 and 120 minutes sent for glucose <sup>s</sup>			X				X	X	
3 point- MMTT at selected sites: Blood samples at 0, 60, and 120 minutes sent for glucose, insulin, and glucagon <sup>s</sup>			X				X	X	
Plasma and Serum for Future Biomedical Research <sup>e</sup>			X				X	X	
Blood (DNA) for Future Biomedical Research <sup>e</sup>			X						
<p>a. The interval between Visit 1 and Visit 2 must be at least 2 weeks and at most 6 weeks.</p> <p>b. This visit is only for subjects who discontinue study medication prematurely. Such subjects should complete procedures for the Early Discontinuation Visit and (if consent was not withdrawn) they should continue to be followed by the investigational site, attending scheduled study visits and undergoing study procedures (other than those related to study medication, or the MMTT), see Section 5.7.1.</p> <p>c. Subjects will be contacted 14 days after the final dose of blinded study drug to collect SAEs.</p> <p>d. A subject ICF must be signed prior to any trial specific procedures being performed and may be signed prior to Visit 1/Screening.</p> <p>e. The Future Biomedical Research (FBR) informed consent must be obtained before FBR samples for DNA analysis, plasma, and serum are collected. The FBR sample for DNA analysis should be obtained pre-dose, at Visit 3/Randomization, as the last sample drawn, on randomized subjects only. The sample may be obtained at a later date during the trial after the FBR informed consent is obtained. The plasma and serum samples for FBR should be collected at Visit 3/Randomization (pre-dose), and Visit 7/Week 24 (or Discontinuation Visit). For the FBR serum and plasma, samples should be collected at all time points, even if the pre-dose or other time point was not collected.</p> <p>f. Subjects on double-blind treatment should be reminded to <b>not take any other AHA medications other than the trial treatments</b> (background metformin and sulfonyleurea (if patient is on an SU), and double-blind study drug) 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.</p> <p>g. Subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at Visit 2; follow-up at other visits may be done by other appropriate site personnel evaluating the subject.</p>									

Trial Period:	Screening	Run-In	Randomization	Double-Blind Treatment				Post-Treatment	
Visit Number	1	2 <sup>a</sup>	3	4	5	6	7	Early Discontinuation	Follow-up
Scheduled Week		-2	0 (Day 1)	4	10	16	24	At time of Discontinuation of study medication <sup>b</sup>	14-Day Post Treatment Telephone Contact <sup>c</sup>
Visit Window Guideline (days)		±5	±5	±7	±7	±7	±7		
<p>h. The witnessed dose will be taken after completion of all procedures for the trial visit, including the collection of all fasting blood samples.</p> <p>i. Not applicable to subjects continuing in the study off of double-blind study medication.</p> <p>j. Full physical examination may exclude genitourinary and rectal exam.</p> <p>k. Brief physical examination includes assessment of heart, lungs, abdomen, extremities and skin.</p> <p>l. ECGs are read locally at the investigative site.</p> <p>m. Site fingerstick A1C is not mandatory, but may be used, at the discretion of the investigator, for screening subjects. However, a fingerstick A1C cannot substitute for a central laboratory measured A1C to determine if a subject meets entry criteria.</p> <p>n. A1C should not be drawn if Discontinuation Visit occurs within six weeks after Visit 3/Randomization (Day 1).</p> <p>o. Fasting C-peptide test at Visit 1/Screening is only for subjects assessed by the investigator as possibly having Type 1 diabetes.</p> <p>p. Includes total cholesterol, high-density lipoprotein (HDL-C) cholesterol, low-density lipoprotein (LDL-C) cholesterol, triglycerides and non-HDL.</p> <p>q. Only subjects with TG meeting the exclusion criterion at Visit 1 should have a repeat test at Visit 2/Week-2, as described in exclusion criterion #15.</p> <p>r. Women of childbearing potential will have a urine pregnancy test (and serum pregnancy test if required by site's Institutional Review Board [IRB]/Ethics Committee [EC]). Subjects with a positive urine pregnancy test during double-blind treatment period will interrupt blinded investigational product and undergo a serum pregnancy test.</p> <p>s. The MMTT will be performed prior to witnessed dose of blinded study drug at Visit 3/Day 1. At Visit 7/Week 24 (or Discontinuation Visit), subjects will take blinded study drug and background metformin and background SU (if applicable) approximately 1-hour before consuming the standard meal (T=0 minutes) for the MMTT. At selected sites, a 3-point MMTT will be performed with measurement of glucose/insulin/glucagon. At all remaining sites, a 2 point MMTT will be performed with measurement of glucose only. For subjects who stop study medication prematurely, the MMTT should be performed at the Discontinuation Visit (and not at Visit 7/Week 24).</p>									

## **7.0 TRIAL PROCEDURES**

### **7.1 Trial Procedures**

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

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

#### **7.1.1 Administrative Procedures**

##### **7.1.1.1 Informed Consent**

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

###### **7.1.1.1.1 General Informed Consent**

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

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

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

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

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

###### **7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research**

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

### **7.1.1.2 Inclusion/Exclusion Criteria**

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

### **7.1.1.3 Subject Identification Card**

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

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. Additionally, for male subjects, sites should indicate if the subject is circumcised or uncircumcised.

### **7.1.1.5 Prior and Concomitant Medications Review**

#### **7.1.1.5.1 Prior Medications**

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

#### **7.1.1.5.2 Concomitant Medications**

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

### **7.1.1.6 Assignment of Screening Number**

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or 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.

### **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  $\geq 7$  days OR compliance  $\leq 75\%$  require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

#### **7.1.1.8.1 Diet and Exercise Counseling and Monitoring**

Refer to Section 5.6 for further details.

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

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

The subject will be instructed to complete the Hypoglycemia Assessment Log (HAL) for any symptomatic episodes he or she believes may represent hypoglycemia. If a fingerstick glucose has been obtained before or shortly (i.e., within a few minutes) after treating, the value should be recorded in the log. In addition, subjects will be instructed to record in the log any fingerstick glucose values  $\leq 70$  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  $\leq 70$  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  $\leq 70$  mg/dL (3.9 mmol/L) regardless of whether they are considered an adverse event, the Hypoglycemia Assessment (HA) eCRF must also be completed. Each event of symptomatic hypoglycemia must be reported as an adverse event on the adverse event eCRF. Each episode of asymptomatic hypoglycemia considered by the Investigator to be an adverse event should also be reported on the adverse event eCRF (see Section 7.1.2.12.2.1 for guidance on reporting).

#### **7.1.1.8.3 Dispense Glucose Meter and SMBG Instructions**

Glucose meters will be supplied to all subjects at Visit 2/Week -2 in order to perform SMBG. Subjects will be instructed on the procedure to perform fingerstick glucose measurements. Subjects will monitor their fingerstick glucose concentrations with a frequency determined appropriate by the investigator (based upon his/her assessment of the subject's risk of increasing or decreasing glucose concentrations) with a minimum of two fasting determinations per week.

During the run-in period, subjects should be counseled to contact the trial site if fingerstick glucose levels are above 270 mg/dL (15.0 mmol/L)  $\geq 2$  times per week. Subjects will be instructed to contact the site if the fingerstick glucose values are  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L). Furthermore, in order to assess for discontinuation from blinded investigational product, subjects should be instructed to contact the site for fingerstick glucose values that are  $>270$  mg/dL (15.0 mmol/L) after Visit 3/Day 1 through Visit 4/Week 4, or  $>240$  mg/dL (13.3 mmol/L) after Visit 4/Week 4 through Visit 5/Week 10, or  $>200$  mg/dL (11.1 mmol/L) after Visit 5/Week 10.

#### **7.1.1.8.4 Witness Dosing**

Administration of blinded study drug will be witnessed by the investigator and/or trial staff at Visit 2/Week -2 (start of the placebo run-in) and at Visit 3/Randomization (Day 1) after completion of all trial procedures, including the collection of all fasting blood samples and performance of the mixed meal tolerance test (MMTT). Additionally, blinded study drug will be witnessed at Visit 7/Week 24 (or Discontinuation Visit) as part of the MMTT.

#### **7.1.1.8.5 Dispense Single-Blind Placebo Run-in Study Drug**

Subjects will be dispensed single-blind study drug (matching placebo tablet for sitagliptin 100 mg and over-encapsulated placebo for dapagliflozin 5 mg) at Visit 2/Week -2 and instructed to take one pill orally per day from each bottle at approximately the same time of day in the morning. The last dose of placebo run-in should be taken on the day prior to Visit 3/Randomization (Day 1).

Refer to Section 5.2.2 for further details.

#### **7.1.1.8.6 Dispense Double-Blind Study Drug**

Subjects will be dispensed double-blind study drug (sitagliptin or matching placebo for sitagliptin and dapagliflozin or matching placebo for dapagliflozin) at all trial visits from Visit 3/Randomization (Day 1) through Visit 6/Week 16 and instructed to take the double-blind study drug once a day, orally at approximately the same time of day in the morning.

Refer to Section 5.2.2 for further detail.

#### **7.1.1.8.7 Medication Compliance Monitoring**

Subjects will be directed to bring any used and unused bottles to each visit. The investigator must maintain a complete and current accountability record for the blinded study drug.

Compliance with the placebo run-in medications should be monitored by study personnel at the site at the end of the placebo run-in at Visit 3/Randomization (Day 1), by comparing the returned single-blind study drug with the amount dispensed and the information reported by the subject. The number of pills issued minus the number of pills returned will be used to calculate pills taken according to the formula below.

$$\text{Compliance} = \frac{\text{pills dispensed} - \text{pills returned}}{\text{No. of days between visits} \times \text{No. of pills taken per day}} \times 100\%.$$

Subjects who are <80% compliant based on pill count with the placebo run-in medication are ineligible for randomization.

During the remainder of 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 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.

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

- Subjects should refrain from nicotine-containing products and/or ingesting caffeine for at least 30 minutes preceding the measurements.
- Subjects should be seated in a chair with their back supported, feet flat on the floor and arm bared (free of restrictions such as rolled up sleeves) and supported at heart level.
- Measurements should begin after at least 5 minutes of rest.
- The appropriate cuff size must be used to ensure accurate measurement. Each subject's cuff size should be noted in his/her source file to assure the same cuff size is used throughout the trial.
- Measurements should be taken on the same arm at each visit (preferably the non-dominant arm).
- Measurements must be taken approximately 2 minutes apart with the duplicate set recorded in the source document and eCRFs.
- Assessment of pulse rate can be manual (rather than using an automated device); however, when done manually, pulse rate must be measured in the brachial/radial artery for at least 30 seconds.

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

#### **7.1.2.2 Postural (Orthostatic) Blood Pressure and Pulse Rate**

Supine and standing blood pressure and pulse rate will be taken in order to evaluate postural changes in blood pressure and pulse rate at the randomization visit and at all subsequent scheduled study visits, as noted in the Trial Flow Chart – Section 6.0. These measurements will be in addition to the sitting blood pressure and pulse rate measurements taken at these clinic visits.

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

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

### **7.1.2.3 Body Weight**

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

- Weight will be taken in duplicate throughout the trial at approximately the same time of day, after voiding (i.e., forced void) and while wearing only a gown and underwear (no shoes or socks). Investigator sites without access to gowns should weigh subjects in light clothing.
- Subjects should be instructed to step gently onto the scale, place both feet together in the center of the scale and stand straight with eyes directed ahead. Subjects should be instructed to stand still and not sway. Measurement will be recorded after the weight has stabilized.
- Body weight should be reported with precision to one decimal place (e.g., 0.1 kg or 0.1 lb). The 2 measurements should be recorded in the source documents. If the 2 measurements differ by more than 0.2 kg or by 0.4 lb, (1) check the subject to ensure proper positioning as indicated above and/or conduct an accuracy check on the scale as instructed below and (2) a different set of duplicate measurements must be obtained, and the 2 new measurements should be recorded in the source documents.

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

### **7.1.2.4 Height**

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

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

A fixed stadiometer with vertical backboard, fixed floorboard and movable headboard should be used. Subjects should stand with the heels of their feet against the vertical backboard with feet pointing outward at approximately a 60-degree angle. Body weight should be distributed evenly with both feet flat on the floor. The examiner should check several contact points with the vertical backboard, including heels, buttocks, shoulder blades, and the back of the head. This may be difficult for subjects with certain body shapes. However, the head should be in the Frankfort plane (an imaginary line from the ear canal to just below the lower orbit of the eye should be parallel to the floor). Subject should be looking straight ahead, and be asked to take a deep breath and stand tall. Once the subject is positioned, the headboard or a flat ruler will be placed on top of the head, with sufficient pressure to compress the hair. The measurement is recorded in cm, to the nearest mm. Measurements will be collected until 2 consecutive measurements do not differ by more than 2.5 cm from each other. The final

height measurement must be recorded. Some people may have physical conditions that may limit the ability to measure height accurately (e.g., kyphosis). In such cases, height should be measured to the best of the examiner's ability, and a note should be made of the condition.

#### **7.1.2.5 Physical Examination**

A complete physical examination will be performed at the Visit 2/Week -2; genitourinary and rectal examination may be omitted from the complete examination. A brief physical examination including assessment of the heart, lungs, abdomen, extremities, and skin will be performed at Visit 7/Week 24 (or Discontinuation Visit). Abnormalities considered clinically significant should be reported as adverse events. Other body systems may be evaluated as per the judgment of the investigator or as needed to evaluate adverse events.

#### **7.1.2.6 12-Lead Electrocardiogram (ECG)**

Single, supine 12-lead ECG will be obtained at Visit 2/Week -2, as 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.

All ECGs performed should be reviewed by the investigator at the investigative site for subject safety monitoring. The investigator is responsible for retaining all copies of the ECG reports.

#### **7.1.2.7 Site Fingerstick A1C Measurement**

Site fingerstick A1C may be used, at the discretion of the investigator, for screening. Central laboratory A1C **MUST** be used to assess inclusion criteria.

#### **7.1.2.8 Fasting Fingerstick Glucose**

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

#### **7.1.2.9 Review of SMBG Measurements and Hypoglycemia Assessment Log**

SMBG measurements and the HAL will be reviewed at all clinic visits and telephone contacts after Visit 2/Week -2 and will be used to assess for events of hypoglycemia, and to determine need for discontinuation from blinded study drug due to hypoglycemia.

#### 7.1.2.10 Assess Subject for Discontinuation Based on Central Laboratory FPG or A1C

During the double-blind treatment period, FPG and A1C values obtained at the central laboratory will be used to assess if the subject meets discontinuation criteria. Refer to Section 5.7 for further details regarding discontinuation.

#### 7.1.2.11 Mixed Meal Tolerance Test (MMTT)

**NOTE: Subjects with hypersensitivity or dietary restrictions to the contents of the nutrition drink or bars may enroll in the trial without participation in the MMTT.**

Sites will be selected to perform either a 2-point or a 3-point MMTT; the type that a site is selected to perform will be based on previous experience in performing MMTTs or other similar testing.

Subjects should be instructed to avoid strenuous exercise for 24 hours prior to their MMTT.

At Visit 3/Randomization (Day 1), the MMTT will be performed prior to the first dose of double blind study drug and metformin (**and SU, for subjects on dual combination metformin and an SU agent**). Subjects' last dose of single-blind placebo run-in medication should be taken in the morning of the day before Visit 3/Randomization [Day 1]).

At Visit 7/Week 24 (or Discontinuation Visit), **subjects will take their blinded study drug and background metformin (and SU, for subjects on dual combination metformin and an SU agent) approximately 1-hour before** consuming the standard meal for the MMTT.

Subjects should remain sitting during the MMTT, with the exception of going to the bathroom. For convenience, an intravenous catheter may be placed in the subject's arm for the collection of blood samples. Insertion of the catheter should occur about 30 minutes before the first scheduled blood draw for the MMTT. The first sample (T=0 minutes) will be drawn immediately prior to administration of the standard meal. The subjects will then consume a standard meal consisting of two nutrition bars and one nutrition drink. This should be ingested within 15 minutes. Blood samples will then be collected as indicated below for either the 2-point or 3-point MMTT. Blood samples collected for the MMTT are separate and distinct from the fasting blood samples done as part of the visit laboratory assessments (i.e., the fasting laboratory assessments cannot be used as the T=0 blood sample for the MMTT).

**NOTE 1:** The subject should consume the entire meal. If the subject is unable to consume at least 1 bar and the entire drink at Visit 3/Randomization (Day 1), the subject should not complete the MMTT and should not participate in the subsequent MMTT (at Visit 7/Week 24 or the Discontinuation Visit). If the subject consumes the minimum requirement for MMTT participation (i.e., at least 1 bar and the entire drink) at Visit 3/Randomization/Day 1 but does not consume the entire meal, the amount of the meal consumed should be recorded and approximately the same proportion of the meal should be consumed for the MMTT at Visit 7/Week 24 (or Discontinuation Visit).

**NOTE 2:** If the subject is unable to consume approximately the same proportion of the meal at Visit 7/Week 24 (or Discontinuation Visit) as they consumed at Visit 3/Randomization (Day 1), the subject should not complete the follow-up MMTT.

**NOTE 3:** Subjects who are discontinuing study medication but agree to continue in the study off of study medication (See Section 5.7.1.2, Discontinuation from Blinded Study Therapy) should have the MMTT conducted at the Discontinuation Visit (See Section 6.0, Trial Flow). These subjects will be requested to return for subsequent study visits with efficacy and safety procedures performed; however, the final visit (i.e., Visit 7/Week 24) MMTT should not be performed.

Guidance for sites performing a 2-point MMTT

Blood samples for the MMTT will be drawn for measurement of glucose at T=0 minutes (immediately prior to meal administration) and then at T=120 minutes following the start of the administration of the meal.

Collect blood samples for the 2-pt MMTT as described in [Table 3](#) below.

Table 3 Timing for the 2-pt MMTT

<b>Timing Relative to Meal Consumption</b>			
	-60 mins	0 mins (immediately before meal)	120 mins
<b>Visit 3/Randomization (Day 1)</b>			
Blinded Study Drug Dosing	None	None	None
Glucose sample collection		X <sup>1</sup>	X
Start Eating Standard Meal <sup>2</sup>		X	
<b>Visit 7/Week 24 (or Discontinuation)</b>			
Blinded Study Drug Dosing	X		
Glucose sample collection		X <sup>1</sup>	X
Start Eating Standard Meal <sup>2</sup>		X	
<sup>1</sup> Samples should be collected immediately before the subject begins to eat the standard meal.			
<sup>2</sup> The subject should completely eat the standard meal over a period of 15 minutes or less.			

Guidance for sites performing a 3-point MMTT

Blood samples for the 3-pt MMTT will be drawn for measurement of glucose, insulin, and glucagon at T=0 minutes (immediately prior to meal administration) and then at T=60 minutes and T=120 minutes following the start of the administration of the meal.

Collect blood samples for the 3-pt MMTT as described in [Table 4](#) below.

Table 4 Timing for the 3-pt MMTT

<b>Timing Relative to Meal Consumption</b>				
	-60 mins	0 mins (immediately before meal)	60 mins	120 mins
<b>Visit 3/Randomization (Day 1)</b>				
Blinded Study Drug Dosing	None	None	None	None
Glucose collection		X <sup>1</sup>	X	X
Insulin collection		X <sup>1</sup>	X	X
Glucagon collection		X <sup>1</sup>	X	X
Start Eating Standard Meal <sup>2</sup>		X		
<b>Visit 7/Week 24 (or Discontinuation)</b>				
Blinded Study Drug Dosing	X			
Glucose collection		X <sup>1</sup>	X	X
Insulin collection		X <sup>1</sup>	X	X
Glucagon collection		X <sup>1</sup>	X	X
Start Eating Standard Meal <sup>2</sup>		X		
<sup>1</sup> Samples should be collected immediately before the subject begins to eat the standard meal.				
<sup>2</sup> The subject should completely eat the standard meal over a period of 15 minutes or less.				

**Standard Meal**

2 nutrition bars

1 nutrition drink

Approximate total nutrient content: (~660 kcal; 96 g carbohydrate, 20 g fat, 28 g protein)

**Note:** The standard meal for the MMTT will be provided or approved by the Sponsor (depending on the country). Please refer to the trial investigator binder for details.

**7.1.2.12 Adverse Event Monitoring**

**7.1.2.12.1 Hyperglycemia**

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

#### 7.1.2.12.2 Hypoglycemia

All episodes considered as likely to represent symptomatic hypoglycemia by the investigator must be captured as an adverse event of "symptomatic hypoglycemia." This diagnosis may be supported by, but does not require, confirmatory blood glucose results (such as those measured using a fingerstick or from a clinical laboratory sample). Further, at the discretion of the investigator, an asymptomatic blood glucose value  $\leq 70$  mg/dL (3.9 mmol/L) may be reported as an adverse event of "asymptomatic hypoglycemia." General guidance regarding the determination as to whether an event is considered to be an adverse event should be followed (see Section 7.2).

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

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

#### 7.1.2.12.3 Urinary Tract Infections

Any subject presenting with symptoms considered to be a urinary tract infection should be recorded as having an adverse event with the term as considered appropriate by the investigator (e.g., cystitis, pyelonephritis, urinary tract infection). The site should collect urine for culture performed by their local laboratory, but urine dipstick should not be performed by the site or local laboratory (since a urinary glucose measurement may provide information suggestive of treatment group assignment). If a urinalysis is clinically necessary, a microscopic urinalysis ONLY and not a dipstick urinalysis should be performed. If symptoms are reported outside of a routine scheduled study visit, clinical assessment and urine testing should be done promptly at an unscheduled visit. The investigator or treating physician should initiate antibiotic treatment as considered clinically appropriate; if possible, a locally obtained culture and sensitivity should be obtained prior to initiating antibiotics. The choice of antibiotic agent and duration of treatment is left to the investigator's or treating physician's discretion.

Additionally, if a subject reports a urinary tract infection treated by another physician, this episode should be captured as an adverse event. The site should attempt to obtain information from the treating physician regarding diagnostic tests performed (excluding urine dipstick results) and treatment provided, and this information should be recorded.

#### 7.1.2.12.4 Genital Fungal Infections

Subjects who suspect that they have a genital fungal infection should be encouraged to report this to investigators. The investigator or treating physician can initiate antifungal treatment either empirically as per local practice or following results from genital swab collected and analyzed by a local laboratory. The choice and duration of antifungal agent used is left to the investigator or treating physician's discretion.

#### **7.1.2.12.5 Reduction in Renal Function**

The investigator should implement an appropriate evaluation for eGFR that may meet discontinuation criteria (as described in Section 5.7) or for events of clinically significant reduction in eGFR (e.g., >30% reduction from baseline values). Such an evaluation should include detailed review of any associated symptoms, thorough review of concomitant medications (including “over the counter” agents) to determine if the subject had any change (new initiation or change in dose) in his or her medication regimen with agents associated with decreases in eGFR (e.g., non-steroidal anti-inflammatory agents, fenofibrate, angiotensin-converting enzyme (ACE) inhibitors, diuretic agents, etc.), and clinical assessment of volume status (e.g., measurement of orthostatic HR and BP, and physical examination focused on assessment of volume status). Additional evaluations, including renal ultrasound, microscopic urinalysis (with culture and sensitivity if infection is considered possible), and urine creatinine and electrolytes should be performed, as clinically appropriate. Any reduction in eGFR that the investigator considers to meet criteria for an adverse event should be reported as an adverse event.

#### **7.1.2.12.6 Ketoacidosis**

In May 2015, the US Food and Drug Administration (FDA) issued a Drug Safety Communication warning that the approved SGLT2 inhibitors, including dapagliflozin, may lead to ketoacidosis. As of the time of approval of this protocol, this issue is still under investigation.

Factors cited by the FDA as potentially triggering the ketoacidosis include major illness and reduced food/fluid intake. According to the FDA communication, patients with ketoacidosis reported in association with SGLT2 inhibitor use had blood glucose levels that were only slightly elevated, compared to typical cases of diabetic ketoacidosis where blood glucose levels are much higher. Investigators should use their clinical judgment to determine if a subject may have signs or symptoms of ketoacidosis and manage as clinically indicated.

#### **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. The optional site fingerstick A1C at Visit 1/Screening, the fasting fingerstick glucose measurement at Visit 3/Randomization, and all urine pregnancy tests will be performed at the investigational site.

Laboratory test results for chemistry, hematology, and lipids will not be masked. Glycemic measurements (e.g., FPG, A1C) will be masked from Visit 3/Randomization (Day 1). However, in order for the investigator to perform an evaluation for discontinuation from the blinded study drug, the central laboratory will report to the investigator in an unmasked manner if an FPG or A1C value meets criteria for discontinuation from blinded study drug criteria (see Sections 5.7).

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

- eGFR <60 mL/min/1.73 m<sup>2</sup>;
- elevations ≥3X ULN in liver transaminases (i.e., ALT and AST) (see Section 12.5 for guidance on retesting);
- elevations in ALT and/or AST ≥3-times the ULN with concurrent total bilirubin ≥2-times the ULN and alkaline phosphatase <2-times the ULN;
- fasting glucose potentially meeting hyperglycemia discontinuation criteria or hypoglycemia discontinuation criteria (see Section 5.7)
- 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 Others)

Laboratory tests for hematology, chemistry and urinalysis are specified in [Table 5](#).

Table 5 Laboratory Evaluations

<b>Hematology</b>	<b>Chemistry</b>	<b>Others</b>
<ul style="list-style-type: none"> <li>• Hemoglobin</li> <li>• Hematocrit</li> <li>• RBC Count</li> <li>• Platelet Count</li> <li>• WBC Count</li> <li>• Neutrophils</li> <li>• Eosinophils</li> <li>• Monocytes</li> <li>• Basophils</li> <li>• Lymphocytes</li> </ul>	<ul style="list-style-type: none"> <li>• BUN</li> <li>• Serum Creatinine (eGFR calculated using the CKD-epi formula)</li> <li>• Calcium (total)</li> <li>• Sodium</li> <li>• Potassium</li> <li>• Chloride</li> <li>• Total Carbon Dioxide (Bicarbonate)</li> <li>• Magnesium</li> <li>• Phosphate</li> <li>• Uric Acid</li> <li>• AST (SGOT)</li> <li>• ALT (SGPT)</li> <li>• Alkaline Phosphatase</li> <li>• Total Bilirubin</li> <li>• Direct (conjugated) Bilirubin<sup>a</sup></li> <li>• Indirect (unconjugated) Bilirubin<sup>a</sup></li> <li>• Albumin</li> <li>• Total Protein</li> </ul>	<ul style="list-style-type: none"> <li>• TSH</li> <li>• Fasting C-peptide</li> <li>• A1C</li> <li>• FPG</li> <li>• Pregnancy Tests (where applicable)</li> <li>• Lipid Panel (i.e., Total Cholesterol, HDL-C, non-HDL-C, LDL-C, and Triglycerides)</li> <li>• Insulin, glucagon (as part of 3-point MTT only)</li> </ul>
<p><sup>a</sup> Both direct and indirect bilirubin measured only when total bilirubin is greater than ULN.</p>		

Laboratory tests will be performed after at least a 10-hour fast (i.e., no food, double-blind study drug, background AHA medication [metformin, sulfonylurea], or drink except water and non-AHA non-study drug as prescribed). Subjects who do not fast before a scheduled visit will be required to return fasting for a study visit within three days. Subjects who have not fasted prior to Visit 1/Screening should obtain a fasting TG and FPG at or prior to Visit 3/Day 1 rather than Visit 1/Screening.

### **7.1.3.2 Future Biomedical Research**

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

- Blood for genomics use
- Plasma for future biomedical research
- Serum for future biomedical research

### **7.1.4 Other Procedures**

#### **7.1.4.1 Withdrawal/Discontinuation**

Subjects who discontinue/withdraw from treatment 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.

Critical Equipment for this trial includes:

- Digital scale

#### **7.1.5 Visit Requirements**

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

##### **7.1.5.1 Fasting Prior to Scheduled Visits**

Subjects should be counseled to fast (i.e., no food, double-blind study drug, background AHA medication [metformin, sulfonylurea], or drink except water and non-AHA non-study drug as prescribed) for at least 10 hours prior to all study visits. Subjects who do not fast before a scheduled visit will be required to return fasting for a study visit within three days. Subjects who have not fasted prior to Visit 1/Screening should obtain a fasting TG and FPG at or prior to Visit 2/Week -2 rather than Visit 1/Screening.

### **7.1.5.2 Scheduling Visits**

At the end of each trial visit, the next trial visit should be scheduled. Every effort should be made to adhere to the visit schedule (see Section 6.0), and in general visits during the double-blind treatment period should be scheduled within +/-7 days (Visit 3/Randomization [Day 1] through Visit 7/Week 24). If unavoidable, a visit may be scheduled at a time outside of this recommended range, but the schedule for subsequent visits must be adjusted so that the total duration of the double-blind treatment period is as close as possible to 24 weeks. Visits should be scheduled relative to the date of Visit 3/Randomization (Day 1). If a visit is scheduled at a time other than the protocol-designated time, careful consideration must be given to the amount of blinded study drug the subject has available.

Trial sites should telephone the IVRS at each of the scheduled subject visits for purposes of enrollment tracking.

Visit 2/Week -2 may be scheduled as soon as it is confirmed that the subject meets all Visit 1/Screening trial criteria, including laboratory criteria, ensuring that the interval between Visit 1 and Visit 2 is **at least 2 weeks** (with a maximum interval of approximately 6 weeks).

The double-blind treatment period begins at Visit 3/Randomization (Day 1). All subsequent double-blind treatment period visits should be scheduled relative to Visit 3/Randomization (Day 1).

### **Visit Reminders-Telephone Contacts**

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

- The date and time of appointment.
- The requirement to fast for at least 10 hours prior to the clinic visit.
- The requirement not to take metformin (or the SU agent, for subjects on metformin and an SU agent) and blinded study drug the morning of the clinic visit. Non-study medications that are not AHA medications should be taken as directed by the prescribing physician.
- The requirement to bring blinded investigational product, open-label metformin, (and the SU agent, for subjects on an SU agent), the blood glucose meter, the HAL and any collected SMBG information to the clinic.
- Prior to MMTT visits only (Visit 3/Randomization and Visit 7 (or Discontinuation): to avoid strenuous exercise for 24 hours prior to the visit.

### **7.1.5.3 Visit 1/Screening**

Subjects must be on a stable metformin dose of  $\geq 1500$  mg for at least 8 weeks at the time of screening alone or in dual combination with an SU (at a dose of  $\geq 50\%$  of maximum labeled dose).

Subjects will be consented and screened according to Visit 1/Screening Inclusion/Exclusion Criteria and will receive a screening number and a Subject Identification Card. The subject's medical history and prior/concomitant medications will be reviewed, and vital signs, body weight, and height will be measured. For subjects assessed as eligible to participate in the trial, fasting blood samples will be obtained. Women of childbearing potential will have a urine pregnancy test performed (and serum pregnancy test if required by site's IRB/EC).

At the site, the investigator may choose to screen subjects with fingerstick A1C measurements (prior to drawing blood samples for the central laboratory screening measurements) to evaluate the likelihood of the subject subsequently meeting trial glycemic inclusion criteria. If, based upon the fingerstick A1C value, the investigator believes the subject is an unlikely candidate for the trial, the subject may be excluded prior to undergoing additional trial procedures. Investigators should be aware that the site-fingerstick A1C is a tool to evaluate a subject's glycemic status and that a central laboratory measured A1C is still required to assess A1C entry criterion at Visit 1/Screening.

**Note (1):** A subject excluded due to the TSH criterion may be re-screened after being on a stable thyroid replacement therapy for at least 6 weeks.

**Note (2):** Subjects with elevated TG levels may have lipid-lowering medication initiated or adjusted and continue in the trial if a repeat measurement at Visit 2/ Week -2 no longer meets the exclusion criterion. Subjects on lipid-lowering medication must be on a stable regimen for at least 4 weeks prior to Visit 3/Day 1.

**Note (3):** Subjects with elevated systolic and/or diastolic blood pressure levels may have blood pressure medication initiated or adjusted and continue in the trial if repeat blood pressure measurements no longer meet the exclusion criterion at **Visit 3/Randomization (Day 1)**. Subjects on blood pressure medication must be on a stable regimen for at least 4 weeks prior to **Visit 3/Randomization (Day 1)**.

#### **7.1.5.4 Visit 2/Week -2: Single-blind Placebo Run-in**

All subjects will be evaluated according to Visit 2/Week -2 Inclusion/Exclusion criteria. The subject's prior/concomitant medications and adverse events will be reviewed; a 12-lead ECG and a full physical exam, including routine vital signs, will be performed; and fasting blood samples obtained. Women of childbearing potential will have a urine pregnancy test performed (and serum pregnancy test if required by site's IRB/EC).

All subjects will (1) have diet/exercise counseling, (2) receive glucose meters and training in performing SMBG, and (3) receive instruction on hypoglycemia symptoms, hypoglycemia management, and completion of the HAL.

Subjects will be instructed to monitor their fingerstick glucose concentrations with a frequency determined appropriate by the investigator (based upon his/her assessment of the subject's glycemic control) but with a minimum of two fasting determinations per week. Subjects are to contact the site if they experience any episodes of hypo- or hyperglycemia.

The first dose of single-blind placebo run-in (matching placebo tablet for sitagliptin and over-encapsulated dapagliflozin placebo) must be taken as a witnessed dose in the clinic visit after completion of all Visit 2/Week -2 procedures, including the collection of all fasting blood samples. Subjects will take their single-blind placebo pills for approximately two weeks prior to randomization. Subjects should be reminded to withhold single-blind study drug on the day of Visit 3/Randomization (Day 1).

#### **7.1.5.5 Treatment Period**

##### **7.1.5.5.1 Visit 3/Randomization (Day 1)**

At Visit 3/ Randomization (Day 1), subjects who meet all trial enrollment criteria will have all baseline laboratory tests and trial procedures performed and will be randomized in a 1:1 ratio to sitagliptin 100 mg q.d. or dapagliflozin 10 mg q.d.

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

The MMTT (either 2-point or 3-point) will be performed as described in Section 7.1.2.11.

Double-blind study drug will be dispensed at Visit 3/Randomization (Day 1). The first dose of double-blind study drug should be taken as a witnessed dose after completion of all trial procedures, including the collection of all fasting blood samples and completion of the MMTT.

##### **7.1.5.5.2 Visit 4/Week 4 through Visit 7/Week 24: Double-blind Treatment Period**

Subjects will be dispensed double-blind study drug at Visit 4/Week 4, Visit 5/Week 10, and Visit 6/Week 16.

Blinded study drug should be taken orally at approximately the same time each morning. If a subject misses a dose of blinded study drug during the trial, they should be instructed to take it as soon as they remember unless it is time for the next dose. Subjects should be instructed not to "make up" for the missed dose by taking two doses at the same time. Compliance with the daily dosed medication during this period will be determined by subject self-report.

##### **7.1.5.6 14-Day Post Treatment Telephone Contact**

A telephone contact will be performed 14 days after the last dose of blinded study drug to collect SAEs.

##### **7.1.5.7 Follow-up for Subjects Who Discontinue Blinded Study Drug**

Subjects who prematurely discontinue blinded study drug should be followed according to Section 5.7.1.

### **7.1.5.8 Follow-up for Subjects Who Discontinue Due to Decreased Renal Function**

Subjects who discontinue blinded study drug for eGFR discontinuation criteria (see Section 5.7) or renal-related adverse events should have a repeat eGFR performed within approximately 1 week after the last dose of blinded study drug. This may be done as part of the Discontinuation Visit (if the Discontinuation Visit occurs within approximately 1 week after the last dose of study drug) or at an unscheduled visit. The out of range test should continue to be repeated at intervals considered appropriate (e.g., weekly or every other week) until the value returns to baseline (pre-randomization value) or a new baseline is established.

## **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 matching placebo or (2) >200 mg/day of sitagliptin or matching placebo for more than 28 days or (3) dosing of >50 mg/day of dapagliflozin or matching placebo.

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).

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

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

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

### **7.2.3 Immediate Reporting of Adverse 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 6](#) 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 6](#). The investigator's assessment of causality is required for each adverse event. Refer to [Table 6](#) for instructions in evaluating adverse events.

Table 6 Evaluating Adverse Events

<b>Maximum Intensity</b>	<b>Mild</b>	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	<b>Moderate</b>	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	<b>Severe</b>	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
<b>Seriousness</b>	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	† <b>Results in death</b> ; or	
	† <b>Is life threatening</b> ; 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	
	† <b>Results in a persistent or significant disability/incapacity</b> (substantial disruption of one's ability to conduct normal life functions); or	
	† <b>Results in or prolongs an existing inpatient hospitalization</b> (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	
	† <b>Is a congenital anomaly/birth defect</b> (in offspring of subject taking the product regardless of time to diagnosis); or	
	<b>Is a cancer</b> (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); or	
	<b>Is associated with an overdose</b> (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.	
<b>Other important medical events</b> 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 †).		
<b>Duration</b>	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
<b>Action taken</b>	Did the adverse event cause the Sponsor's product to be discontinued?	
<b>Relationship to Sponsor's Product</b>	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	
	<b>The following components are to be used to assess the relationship between the Sponsor's product and the AE</b> ; 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:	
	<b>Exposure</b>	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?
	<b>Time Course</b>	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)?
	<b>Likely Cause</b>	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

<b>Relationship to Sponsor's Product (continued)</b>	<b>The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)</b>	
	<b>Dechallenge</b>	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.)
	<b>Rechallenge</b>	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.
	<b>Consistency with Trial Treatment Profile</b>	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.		
<b>Record one of the following:</b>		<b>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).</b>
<b>Yes, there is a reasonable possibility of Sponsor's product relationship.</b>		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.
<b>No, there is not a reasonable possibility of Sponsor's product relationship</b>		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 are 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. Separate analysis plans (i.e., separate documents from the sSAP) will be developed to detail other planned analyses (i.e., future biomedical research).

### 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.

<b>Study Design Overview</b>	Sitagliptin vs. dapagliflozin as add-on to metformin alone or in dual combination with an SU agent in subjects with mild renal impairment
<b>Treatment Assignment</b>	Subjects will be randomized in a 1:1 ratio to sitagliptin or dapagliflozin. Stratification factors: No stratification factors
<b>Analysis Populations</b>	Efficacy: Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
<b>Primary Endpoint(s)</b>	A1C – change from baseline at Week 24
<b>Key Secondary Endpoints</b>	Change from baseline at Week 24 in each of the following: <ul style="list-style-type: none"><li>• Post-prandial glucose excursion (PPGE) (increment in glucose from T=0 to T=120 minutes)</li><li>• Post-prandial glucose (PPG) (glucose value at T=120 minutes)</li><li>• Glucagon Area Under the Curve (AUC)</li><li>• Insulin AUC</li><li>• Insulin AUC to Glucagon AUC ratio</li><li>• FPG</li></ul> Proportion of subjects with A1C <7% at Week 24

<p><b>Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses</b></p>	<p>The primary efficacy analysis will compare the efficacy of sitagliptin relative to dapagliflozin in change from baseline in A1C at Week 24. The mean change from baseline in A1C at Week 24 with sitagliptin will be compared to that of dapagliflozin via a cLDA model.</p> <p>For the primary hypothesis, sitagliptin will be considered non-inferior to dapagliflozin if the upper bound of the two-sided 95% confidence interval (CI) of the between-group difference in LS mean change from baseline in A1C (sitagliptin minus dapagliflozin) is less than 0.3% (the non-inferiority margin).</p> <p>If the non-inferiority hypothesis is rejected, and if the upper bound of the two-sided 95% CI of the between-group difference in LS mean change from baseline in A1C (sitagliptin minus dapagliflozin) is less than 0, sitagliptin will be considered superior to dapagliflozin in lowering A1C.</p>
<p><b>Statistical Methods for Key Safety Analyses</b></p>	<p>No tier 1 safety endpoints are pre-specified in this study. 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 [15]</p>
<p><b>Interim Analyses</b></p>	<p>No interim analysis is planned.</p>
<p><b>Multiplicity</b></p>	<p>The study-wise type I error rate will be controlled at <math>\alpha=0.025</math> (one-sided) using an ordered testing procedure.</p> <p>The study will first test for non-inferiority for A1C. If the success criterion for non-inferiority is met, superiority for A1C will be assessed. If the test for superiority is successful, the secondary hypothesis for post-prandial glucose excursion will be tested. All three tests will be conducted at <math>\alpha=0.025</math> (one-sided).</p>
<p><b>Sample Size and Power</b></p>	<p>The planned sample size is 278 subjects per treatment group. The trial has &gt;99% power to establish that sitagliptin is non-inferior to dapagliflozin in lowering A1C at an overall one-sided, 2.5% <math>\alpha</math>-level, if the underlying treatment difference is 0%.</p>

**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 important 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 (sitagliptin minus dapagliflozin) 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.

#### 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 7. These endpoints will be analyzed at Week 24.

Table 7 Efficacy Endpoints

<b>Primary Endpoint</b>
Change from Baseline in A1C at Week 24
<b>Secondary Endpoints</b>
Change from Baseline in PPGE (increment in glucose from T=0 to T=120 minutes) at Week 24
Change from Baseline in 2- hour PPG (glucose value at T=120 minutes) at Week 24
In a subset of subjects who undergo the 3-point MMTT
Change from Baseline in Glucagon AUC <sub>0-120 min</sub> at Week 24
Change from Baseline in Insulin AUC <sub>0-120 min</sub> at Week 24
Change from Baseline in Insulin AUC <sub>0-120 min</sub> to Glucagon AUC <sub>0-120 min</sub> Ratio at Week 24
Proportion of subjects with A1C < 7.0% at Week 24
Change from Baseline in FPG at Week 24

#### 8.4.2 Safety Endpoints

The descriptions of the safety measurements and time points at which they are measured are described in Section 4.2.3.2 and Section 6.0 (Trial Flow Chart), respectively. The safety endpoints to be analyzed are listed in Table 9 in section 8.6.2. These endpoints will be analyzed over 24 weeks.

### **8.4.3 Derivation of Efficacy Endpoints**

Computation details for endpoints listed in [Table 7](#) are provided below

- Post Prandial Glucose Excursion = Glucose at 120 minutes – glucose at 0 minutes from the start of the meal. PPGE will be considered missing if measurement at one time point is missing.
- AUC endpoints will be derived via the trapezoidal rule using the 0-, 60-, and 120-minute measurements from the start of the meal during the 3-point MMTT. AUC will be considered missing if any of those 3 measurements is missing.

### **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.

#### **8.5.1 Efficacy Analysis Populations**

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized subjects who:

- receive at least one dose of study treatment,
- have at least one observation for the analysis endpoint, at baseline or subsequent to at least one dose of study treatment

A secondary population for analyzing primary and key secondary efficacy endpoints at Week 24 will be the Per-Protocol (PP) population. All randomized subjects who take at least one dose of study medication, with a measurement of the analysis endpoint at both baseline and the time point of interest (Week 24), without any of the following protocol deviations will be included in this population:

- Drug compliance <75%, using the compliance definition provided in Section 8.11.
- Use of prohibited antihyperglycemic medications (found in Section 5.5) after randomization for a total of  $\geq 14$  days or  $\geq 7$  consecutive days
- Use of pharmacologic doses of corticosteroids for  $\geq 2$  consecutive weeks after randomization
- Incorrect double-blind study drug, or a change in metformin dose or SU dose (if applicable) after randomization, for  $\geq 14$  consecutive days.

Data after the last dose of study medication plus an offset of 5 days will be excluded from all efficacy analyses, with the exception of selected sensitivity analyses to be described in the sSAP.

These protocol deviations are not just a repetition of the exclusion and inclusion criteria in the protocol, but a clinical assessment of deviations from the protocol-specified criteria that will either affect or confound the measures of efficacy. Any subject meeting any of the above criteria during the trial will be excluded from the PP population.

The final determination on major protocol deviations, and thereby the composition of the PP population, will be made prior to the final unblinding of the database and will be documented in a separate memo. Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using both the FAS and Per-Protocol populations. Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

### **8.5.2 Safety Analysis Populations**

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. This will be the randomized treatment group for all subjects except those who take incorrect study treatment for the entire treatment period. Such subjects will be included in the treatment group corresponding to the study treatment actually received.

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

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 Statistical Methods.

## **8.6 Statistical Methods**

Statistical testing and inference for safety analyses are described in 8.6.2. Efficacy 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. All statistical tests will be conducted at  $\alpha=0.025$  (one-sided) level.

### **8.6.1 Statistical Methods for Efficacy Analyses**

This section describes the statistical methods that address the primary and secondary objectives.

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

- Target population: Patients with T2DM and mild renal impairment who have inadequate glycemic control on metformin alone or in dual combination with an SU agent
- Endpoint: Mean change from baseline (in A1C, in incremental post-prandial glucose excursion) at Week 24
- Measure of intervention effect: Difference in the effect of randomized treatments on the endpoint if all subjects remained on treatment through Week 24

For the analysis of change from baseline in A1C, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [13] will be used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will also adjust for treatment, time, background AHA (metformin alone, or metformin in combination with an SU agent), the interaction of time by background AHA, and the interaction of time by treatment. The treatment difference in terms of mean change from baseline at Week 24 will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

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

Analyses of the change from baseline in other continuous efficacy endpoints at Week 24 will be performed using the cLDA model as described above.

An ANCOVA model as described above will also be used in the PP population as an additional sensitivity analysis for the primary and key secondary endpoints at Week 24. By definition, there will be no missing outcome data in the PP population.

For the analysis of percentages of individuals at the A1C goal of <7.0% (53 mmol/mol) at Week 24, the cLDA model that is used for the analysis of A1C will also be used to impute the missing data on A1C. 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 24 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 imputations (MI) techniques proposed by Rubin [14] to yield an overall estimate of the response rate and associated variance for each group. The estimated response rates and adjusted effective sample sizes [15] will then be used to obtain the confidence interval for between-group rate difference via M&N method.

A sensitivity analysis for the A1C goal of <7.0% will also be performed, with imputation of “Missing=Not at Goal”. The percentages of subjects at target A1C control at Week 24 will be analyzed assuming that all missing Week 24 A1C values were not at target.

Table 8 summarizes the key efficacy analyses.

Table 8 Analysis Strategy for Key Efficacy Variables

Endpoint	Primary vs. Supportive Approach <sup>†</sup>	Statistical Method	Analysis Population	Missing Data Approach
<b>Primary Endpoint/Primary Hypothesis</b>				
Change from baseline in A1C at Week 24	P	cLDA	FAS	Model-based
	S	ANCOVA	PP	N/A
<b>Secondary Endpoint/Secondary Hypothesis</b>				
Change from baseline in PPGE (increment in glucose from T=0 to T=120 minutes) at Week 24	P	cLDA	FAS	Model-based
	S	ANCOVA	PP	N/A
<b>Other Secondary Endpoints</b>				
Change from baseline in 2-hr PPG (glucose value at T=120 minutes) at Week 24	P	cLDA	FAS	Model-based
	S	ANCOVA	PP	N/A
Change from baseline in glucagon AUC <sub>0-120min</sub> at Week 24	P	cLDA	FAS	Model-based
	S	ANCOVA	PP	N/A
Change from baseline in insulin AUC <sub>0-120min</sub> at Week 24	P	cLDA	FAS	Model-based
	S	ANCOVA	PP	N/A
Change from baseline in the insulin AUC <sub>0-120min</sub> to glucagon AUC <sub>0-120min</sub> ratio at Week 24	P	cLDA	FAS	Model-based
	S	ANCOVA	PP	N/A
Proportion of subjects with A1C < 7.0% at Week 24	P	M&N	FAS	MI
	S	M&N	FAS	Missing=Not at Goal
Change from baseline in FPG at Week 24	P	cLDA	FAS	Model-based
	S	ANCOVA	PP	N/A
<sup>†</sup> P=Primary approach; S=Supportive approach. A1C=Glycosylated hemoglobin; ANCOVA=Analysis of covariance; cLDA=Constrained longitudinal data analysis; FAS=Full analysis set; =Fasting plasma glucose; N/A=Not applicable; P=Primary; PPG=Post-Prandial Glucose; S=Supportive; M&N= Miettinen and Nurminen; MI=Multiple Imputations				

### **Missing Data Handling**

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. Reasons for discontinuation from the study may include lack of efficacy, clinical or laboratory adverse experiences, relocation, withdrawal of consent, protocol deviations, and/or data processing issues. Missing data caused by relocation and data processing issues are likely to be MCAR. On the other hand, missing data caused by discontinuation due to lack of efficacy may belong to MAR because the discontinuation may depend on the observed efficacy outcomes. The MAR or MNAR mechanisms might each underlie the other reasons to some extent. If treatment in large part determines the loss of data for these other reasons (such as clinical or laboratory adverse experiences), the mechanism may be close to MAR because treatment assignment is an observed variable and included in the analysis model. Based on prior study results, missing data due to other reasons is relatively infrequent.

For the analysis of change from baseline in A1C, additional analyses will be performed, with specific details for these models provided prior to unblinding:

- Analyses that assume that the distribution of the missing data differs from the distribution of the observed data will be run. Different assumptions for the missing data distribution will be considered, including MNAR.
- If >5% of the subjects in any treatment group were <75% compliant with study medication (using the definition in Section 8.11), at least one model will account for compliance.

Details describing the sensitivity analyses will be provided in the sSAP. Further investigation will be performed if the results from these sensitivity analyses are not consistent with results from the primary analyses.

The strategy to address multiplicity issues with regard to multiple hypotheses is described in Section 8.7 Interim Analyses and 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 experiences (AEs), laboratory tests, vital signs, and ECG measurements.

The following analysis approaches will be used:

- The primary analysis approach will consider all on-treatment data and data up to and including 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 9). The tiers differ with respect to the analyses that will be performed. No safety parameters have been identified as "Tier 1" safety endpoints. Therefore all safety endpoints 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 are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory and vital signs parameters 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 will belong to Tier 3.

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 less 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.

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. Mean change from baseline over time will be plotted with the corresponding standard errors.

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, documented hypoglycemia AEs will also be considered Tier 2 endpoints. The 95% confidence intervals will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method [15], an unconditional, asymptotic method.

Table 9 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint <sup>†</sup>	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	There are no pre-determined Tier 1 endpoints		
Tier 2	Any AE <sup>†</sup>	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
	AEs of hypoglycemia	X	X
	AEs of documented hypoglycemia	X	X
	AEs of severe hypoglycemia	X	X
	Any	X	X
	Requiring medical assistance	X	X
	Not requiring medical assistance	X	X
	Specific AEs <sup>†</sup> , SOCs, or PDLCs (incidence $\geq$ 4 subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs <sup>‡</sup> (incidence <4 of subjects in all of the treatment groups)		X
	Additional hypoglycemia endpoints		X
	Change from Baseline Results (Laboratory measurements, Vital Signs)		X
<sup>†</sup> Adverse Experience references refer to both Clinical and Laboratory AEs. <sup>‡</sup> Includes only those endpoints not already pre-specified as Tier-2 endpoints. SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.			

**Analysis of Hypoglycemia**

The analysis of hypoglycemia will be performed separately by background AHA, i.e., for patients on metformin alone or metformin in combination with an SU agent.

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

- Adverse events of hypoglycemia (symptomatic or asymptomatic), regardless of biochemical documentation.
- Adverse events of documented hypoglycemia, defined as adverse events of symptomatic hypoglycemia with a concurrent glucose measurement of  $\leq$ 70 mg/dL ( $\leq$ 3.9 mmol/L).
- Adverse events of severe hypoglycemia, defined as adverse events of symptomatic hypoglycemia that required assistance, either medical or non-medical, regardless of whether such assistance was obtained, and regardless of biochemical documentation. These events will be further sub-classified as:
  - Those that required medical assistance. Adverse events of symptomatic hypoglycemia that included a markedly depressed level of consciousness, loss of consciousness, or seizure will be classified as having required medical assistance, whether or not medical assistance was obtained

- Those that did not require medical assistance (i.e., those episodes that required non-medical assistance to treat).

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

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

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

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

### **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<sup>2</sup>).
- Categorical baseline demographic variables: age (<35 years, ≥35 and <45 years, ≥ 45 and <55 years, ≥55 and <65 years, ≥65 and <75 years, ≥75 years), gender (male, female), and race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Multi-Racial), ethnicity (Hispanic/Latino or not).
- Baseline A1C, and distribution of A1C at baseline (A1C levels <8%, and ≥8%)
- Baseline FPG
- Baseline eGFR
- Time since diagnosis of diabetes mellitus (years)
- Geographic region (Americas, Europe, Asia, Other)
- Background AHA (metformin alone, or metformin in dual combination with an SU agent)

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**

The study-wise type I error rate will be controlled at  $\alpha=0.025$  (one-sided) using an ordered testing procedure.

The study will first test for non-inferiority for A1C. If the success criterion for non-inferiority is met, superiority for A1C will be assessed. If the test for superiority is successful, the secondary hypothesis for post-prandial glucose excursion will be tested. All three tests will be conducted at  $\alpha=0.025$  (one-sided).

## 8.9 Sample Size and Power Calculations

This study will randomize approximately 556 subjects (in a 1:1 ratio) into the sitagliptin group and dapagliflozin group and has >99% power to establish that sitagliptin is non-inferior to dapagliflozin in lowering A1C at an overall one-sided, 2.5%  $\alpha$ -level, if the underlying treatment difference is 0%.

The power and sample size are based on the following assumptions derived using data from MK-0431 Protocol 020 and published data for dapagliflozin:

- 1) The cumulative attrition rates for each group at Weeks 6, 12, 18, and 24 are 0.03, 0.05, 0.08, and 0.11.
- 2) The conditional correlation matrix (correlation matrix of the post-randomization measurements conditional on the baseline value) at Weeks 6, 12, 18, and 24 is

1.00	0.67	0.56	0.50
0.67	1.00	0.86	0.76
0.56	0.86	1.00	0.90
0.50	0.76	0.90	1.00

- 3) The conditional standard deviation is 0.7%

The non-inferiority margin is regarded as a minimum clinically important difference between the 2 treatments. The calculation is based on the two-sample t-test with an effective sample size of 261 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 difference is < 0.3%. Given the assumed SD of changes from baseline in A1C, the half-width of the 95% CI for the between-group difference (sitagliptin minus dapagliflozin) is expected to be 0.12% (based on the assumptions used in the power computation); thus, if the observed between-group difference is less than 0.18%, the success criterion of non-inferiority will be met.

If the non-inferiority null hypothesis is rejected, superiority for A1C will be tested.

If the A1C superiority test is rejected, superiority for PPGE (increment in glucose T=0 to T=120 minutes) will be tested. This study has 82% power to demonstrate the superiority of sitagliptin over dapagliflozin in lowering PPGE at a one-sided, 2.5%  $\alpha$ -level, if the underlying treatment difference in PPGE is 12.0 mg/dL and an assumed standard deviation of 45.0. These results are based on MK-0431 P020 and canagliflozin study 3006.

A sample size of approximately 120 subjects/group for the subset of subjects who will undergo the 3-point MTT will provide approximately 90% power to detect a treatment difference of 20.0 pg-h/ml for glucagon AUC.

## 8.10 Subgroup Analyses and Effect of Baseline Factors

No subgroup analyses are planned for this study.

### **8.11 Compliance (Medication Adherence)**

The computation of compliance in the All Subjects Treated (AST) set will be based on the study medication case report form. Both the assigned treatment and any matching placebo pills 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, defined as follows:

- For the sitagliptin group, a subject is compliant if the subject took exactly one 1 tablet of sitagliptin 100 mg and 1 capsule of matching placebo to dapagliflozin
- For the dapagliflozin group, a subject is compliant if the subject took:
  - 1 capsule of dapagliflozin 5 mg and 1 tablet of matching placebo to sitagliptin from Visit 3/Day 1 through one day prior to Week 4/Visit 4
  - 1 capsule of dapagliflozin 10 mg (or 5 mg if the patient was unable to tolerate dapagliflozin uptitration) and 1 tablet of matching placebo to sitagliptin from Week 4/Visit 4.

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 dapagliflozin or sitagliptin.

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.

Summary statistics (N, proportion) of subjects who could not tolerate dapagliflozin 10 mg will also be provided.

## **9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES**

### **9.1 Investigational Product**

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

Clinical Supplies will be provided by the Sponsor as summarized in [Table 10](#).

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

Table 10 Product Descriptions

<b>Product Name &amp; Potency</b>	<b>Dosage Form</b>
Sitagliptin 100mg	Tablet
Dapagliflozin 5mg	Capsule
Dapagliflozin 10mg	Capsule
Placebo to match Sitagliptin 100mg	Tablet
Placebo to match Dapagliflozin 5 & 10mg	Capsule

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

### **9.2 Packaging and Labeling Information**

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

Subjects will receive single blind supplies for two weeks in finished good bottles which contain 21 tablets or capsules. Subjects will receive double blind supplies for intervals of 4 weeks, 6 weeks or 8 weeks throughout the 24 week period of double blind treatment in finished good bottles containing 35 or 63 count of tablets or capsules or the matching placebo.

### **9.3 Clinical Supplies Disclosure**

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 or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

## **10.3 Compliance with Law, Audit and Debarment**

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor 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](http://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](http://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](http://www.clinicaltrials.gov) if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

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

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

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

## **11.0 LIST OF REFERENCES**

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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.<sup>1</sup>
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.<sup>2</sup>
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.<sup>2</sup>
- 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 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 Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

### **3. Summary of Procedures for Future Biomedical Research**

#### **a. Subjects for Enrollment**

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

**4. Confidential Subject Information for Future Biomedical Research**

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

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

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

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

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

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

## **5. Biorepository Specimen Usage**

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

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

## **6. Withdrawal From Future Biomedical Research**

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

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

## **7. Retention of Specimens**

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

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

## **8. Data Security**

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

## **9. Reporting of Future Biomedical Research Data to Subjects**

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

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

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

## **10. Gender, Ethnicity and Minorities**

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

## **11. Risks Versus Benefits of Future Biomedical Research**

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

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

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

## **12. Self-Reported Ethnicity**

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

## **13. Questions**

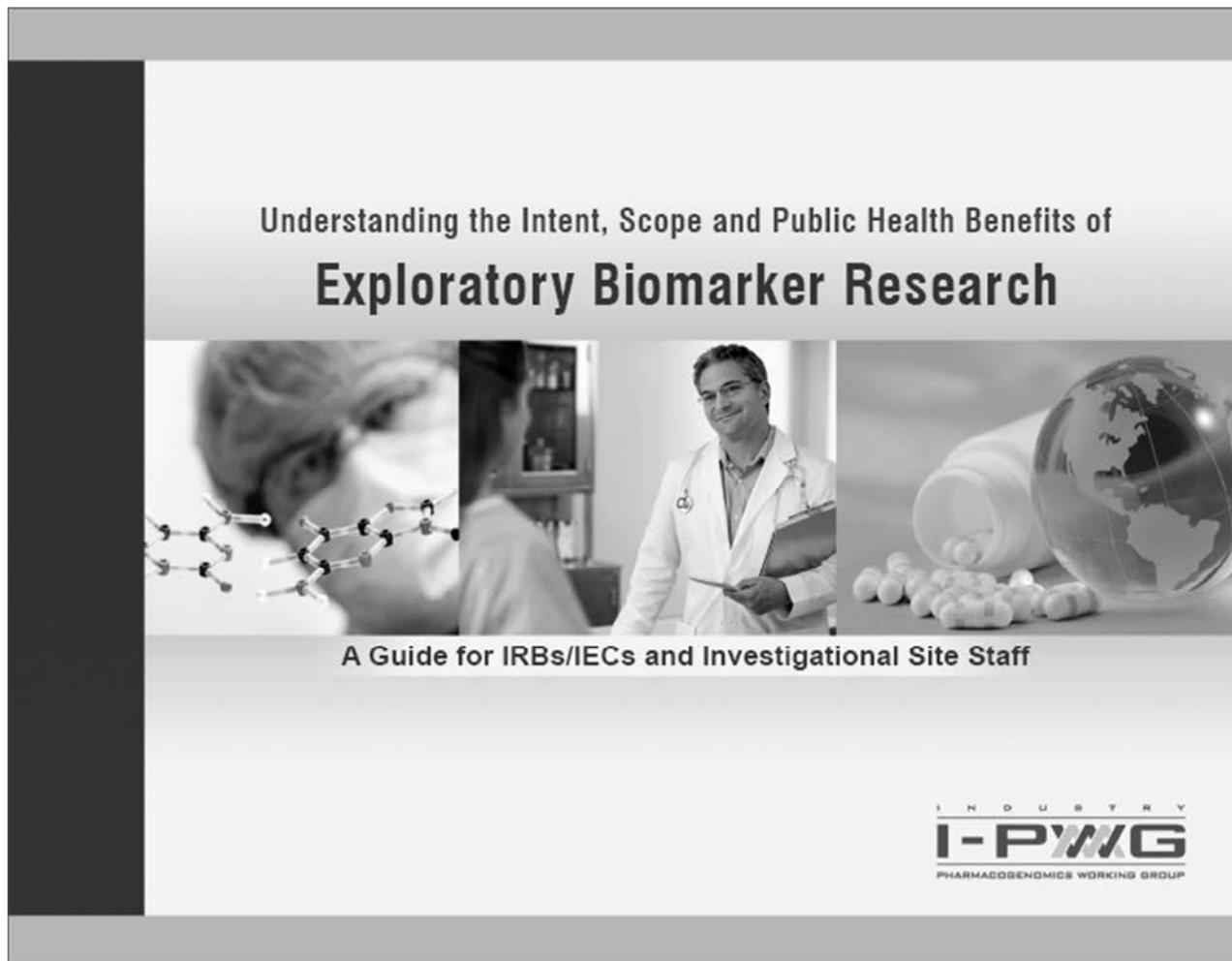
Any questions related to the future biomedical research should be e-mailed directly to

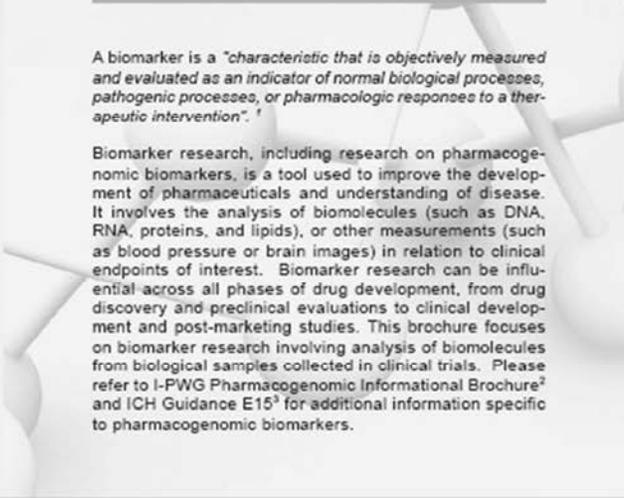
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2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; <http://www.ich.org/LOB/media/MEDIA3383.pdf>

### 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](http://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".<sup>1</sup>

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<sup>2</sup> and ICH Guidance E15<sup>3</sup> 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.<sup>4</sup> 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/](http://www.fda.gov/oc/initiatives/criticalpath/); in the EU: [www.imi.europa.eu/index\\_en.html](http://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).<sup>5</sup> 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](http://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.<sup>3, 4-6</sup>

### 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.<sup>7</sup> 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.

### 5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.<sup>26</sup> 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<sup>®</sup>) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec<sup>®</sup>) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix<sup>®</sup>) or cetuximab (Erbix<sup>®</sup>) 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<sup>®</sup>) 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<sup>®</sup>).

**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<sup>®</sup>), 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 sur-

rogates 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<sup>™</sup> 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.<sup>26-27</sup>

### 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

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.<sup>26-31</sup>

#### 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

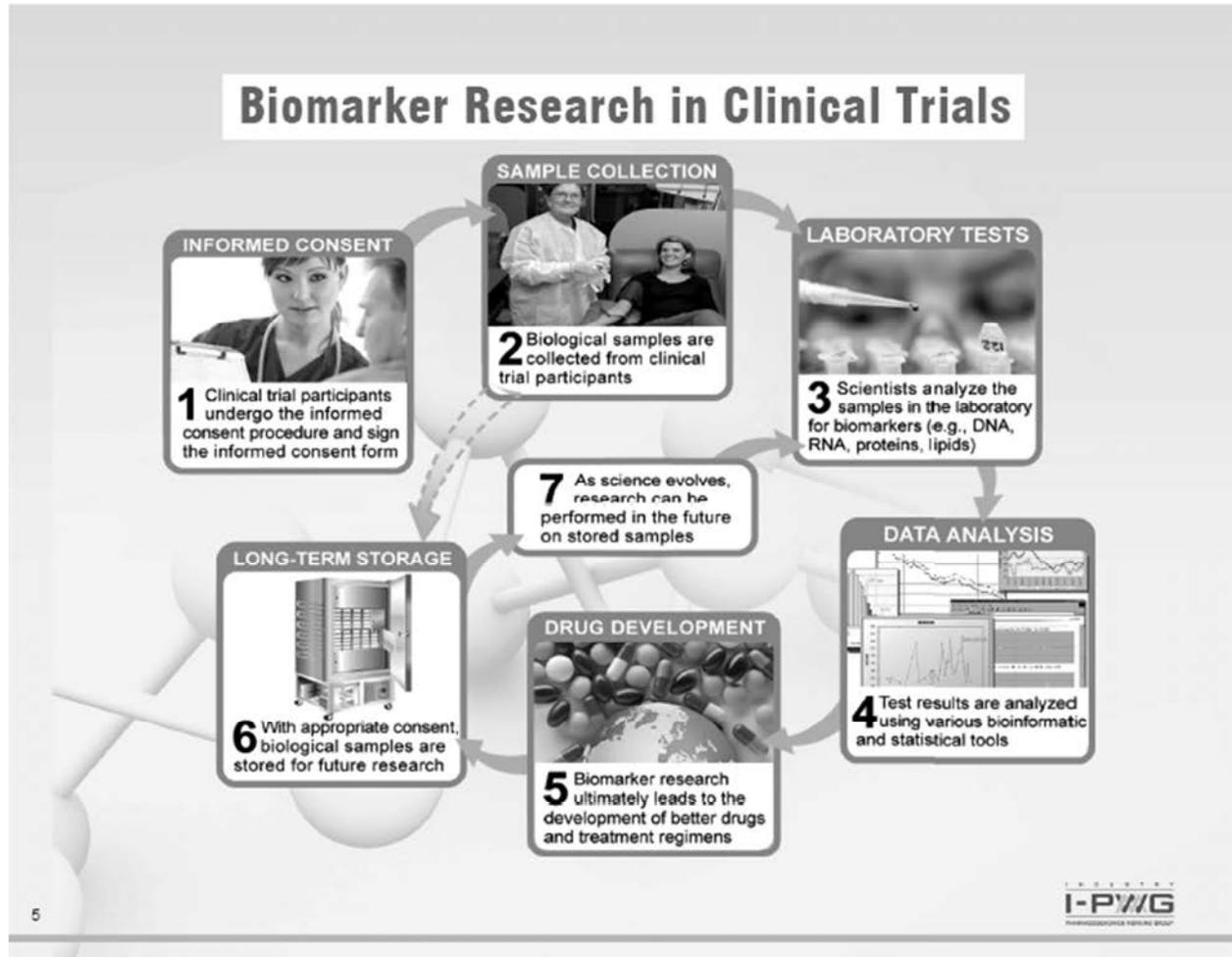
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants 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.<sup>3, 31</sup> 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:<sup>30</sup>

**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.<sup>3</sup> 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.<sup>38</sup>

**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.



### 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.* 2008 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.<sup>34-35</sup>

### 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 (Erbix<sup>®</sup>) and panitumumab (Vectibix<sup>®</sup>) 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.<sup>28,33</sup> 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.<sup>28,32</sup>

#### 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

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."*<sup>31</sup>

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).<sup>36-37</sup>

### 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](http://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-



ities and policy groups to ensure alignment. More information about the I-PWG is available at: [www.i-pwg.org](http://www.i-pwg.org).

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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 $\geq 3X$ ULN

Increases in ALT or AST  $\geq 3X$  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  $\geq 3X$  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)  $\geq 2X$  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 $\geq 3X$ ULN*

##### **A) Subject has:**

- **ALT or AST  $\geq 3X$  ULN with TBL  $\geq 2X$  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  $\geq 8X$  ULN

**OR**

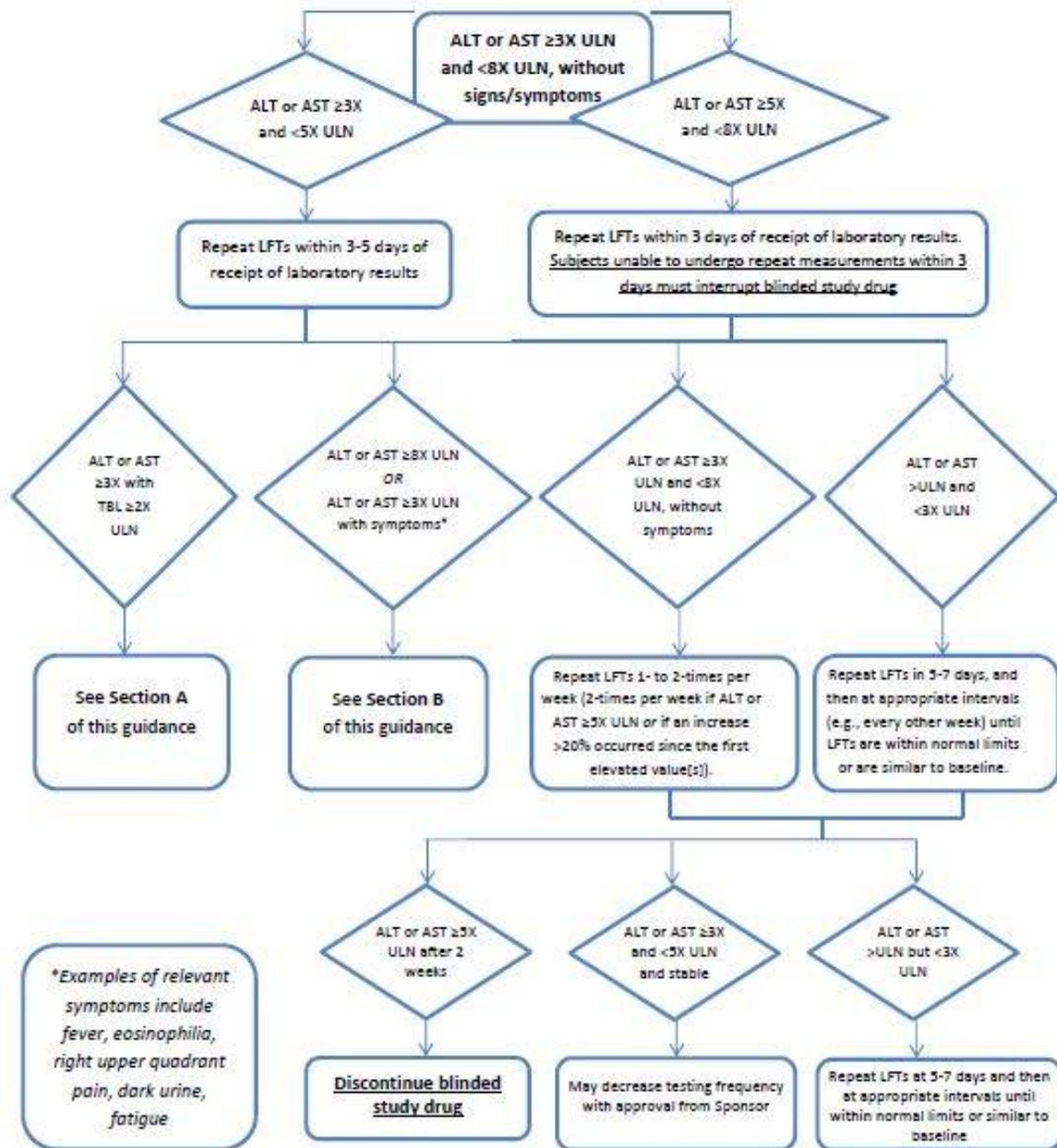
- ALT or AST  $\geq 3X$  ULN and  $< 8X$  ULN, with signs or symptoms of a drug reaction consistent with liver injury (e.g., fever, eosinophilia, right upper quadrant pain, dark urine, fatigue, etc.)

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  $\geq 3X$  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  $\geq 3X$  ULN with TBL  $\geq 2X$  ULN and alkaline phosphatase  $< 2X$  ULN and without an established etiology
- ALT or AST  $\geq 8X$  ULN or  $\geq 3X$  ULN with symptoms consistent with liver injury and without an established etiology
- ALT or AST  $\geq 5X$  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 (PDLIC)

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 <sup>†</sup> Criterion	Categories Assessed for Each Criterion	
		At Least One Value	Last On-Treatment Value
<b>Laboratory – Hematology</b>			
Hemoglobin (g/dL)	1. Decrease $\geq$ 1.5 g/dL 2. Increase $>$ 2.0 g/dL 3. Increase $>$ 2.0 g/dL and value $>$ ULN	Y Y Y	Y Y Y
WBC Count ( $10^3$ /microL)	1. Decrease $\geq$ 50% and value $<$ LLN 2. Increase $\geq$ 20% and value $>$ ULN	Y Y	Y Y
Neutrophil Count ( $10^3$ /microL)	1. Decrease $\geq$ 20% and value $<$ LLN 2. Increase $\geq$ 20% and value $>$ ULN	Y Y	Y Y
Lymphocyte Count ( $10^3$ /microL)	1. Decrease $\geq$ 20% and value $<$ LLN 2. Increase $\geq$ 20% and value $>$ ULN	Y Y	Y Y
Platelet Count ( $10^3$ /microL)	1. Decrease $\geq$ 25% and value $<$ LLN 2. Increase $\geq$ 100% and value $>$ ULN	Y Y	Y Y
<b>Laboratory – Chemistry</b>			
BUN (mg/dL)	1. Increase $\geq$ 50% and value $>$ ULN	Y	Y
eGFR	1. Decrease $>$ 30% 2. Decrease $>$ 50%	Y Y	Y Y
Total Bilirubin (mg/dL)	1. Value $>$ 2x ULN	Y	Y
AST (IU/L)	1. Value $\geq$ 3x ULN 2. Value $>$ 5x ULN 3. Value $>$ 10x ULN 4. Value $>$ 20x ULN	Y Y Y Y	Y Y Y Y
ALT (IU/L)	1. Value $\geq$ 3x ULN 2. Value $>$ 5x ULN 3. Value $>$ 10x ULN 4. Value $>$ 20x ULN	Y Y Y Y	Y Y Y Y
AST (IU/L) or ALT (IU/L)	1. Value $\geq$ 3x ULN 2. Value $>$ 5x ULN 3. Value $>$ 10x ULN 4. Value $>$ 20x ULN	Y Y Y Y	Y Y Y Y
AST (IU/L) or ALT (IU/L)+ Total Bilirubin (mg/dL)	1. ALT $\geq$ 3 $\times$ ULN or AST $\geq$ 3 $\times$ ULN with concurrent Bilirubin $>$ 2 $\times$ ULN	Y	Y
Alkaline Phosphatase (IU/L)	1. Value $>$ 1.5x ULN	Y	Y
Serum Uric Acid (mg/dL)	1. Increase $\geq$ 50% and value $>$ ULN	Y	Y
Serum Sodium (mEq/L)	1. Decrease $\geq$ 10 mEq/L and value $<$ LLN 2. Increase $\geq$ 10 mEq/L and value $>$ ULN 3. Value $>$ 155 mEq/L	Y Y Y	Y Y Y
Serum Potassium (mEq/L)	1. Decrease $\geq$ 1.0 mEq/L and value $<$ LLN 2. Increase $\geq$ 1.0 mEq/L and value $>$ ULN 3. Value $>$ 5.4 mEq/L and value increased by 15%.above baseline 4. Value $\geq$ 6.0 mEq/L	Y Y Y Y	Y Y Y Y
Serum Calcium (mg/dL)	1. Increase $\geq$ 1.0 mg/dL and value $>$ ULN 2. Decrease $\geq$ 1.0 mg/dL and value $<$ LLN	Y Y	Y Y

<b>ECG</b>			
Serum Magnesium	1. Increase $\geq 1.0$ mg/dL and value > ULN	Y	Y
	2. Decrease $\geq 1.0$ mg/dL and value < LLN	Y	Y
Serum Phosphate	1. Increase $\geq 0.5$ mg/dL and value > ULN	Y	Y
	2. Decrease $\geq 0.5$ mg/dL and value < LLN	Y	Y
† Increases and decreases are relative to baseline. ‡ LLN = Lower limit of normal. § ULN = Upper limit of normal.			

“At Least One Value” will include results meeting the PDLC criterion at any time during the Treatment Period (defined as the period from randomization up to 5 days after the final dose of study medication). “Last On-treatment Value” will include only the last available result during the Treatment Period. A listing of all post Treatment Period values that meet PDLC criteria will also be provided.

### 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	

## MK-0431-838 – EudraCT No.: 2014-005525-13

Study Title: A Phase III, Multicenter, Randomized, Double-Blind, Active-Comparator Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Sitagliptin Compared with the Addition of Dapagliflozin in Subjects with Type 2 Diabetes Mellitus and Mild Renal Impairment Who Have Inadequate Glycemic Control on Metformin

### Local Protocol Addendum for Norway - Protocol MK-0431-838-00 and potential amendments.

If the subject is of reproductive potential and is not surgically sterile, the subject must be willing to use **two** methods of birth control starting from the time of consent through 14 days after the completion of the study.

The **two** birth control methods can either be two barrier methods **or** a barrier method plus a hormonal method to prevent pregnancy.

The following are considered adequate barrier methods of contraception: condom (by male partner) and copper intrauterine device.

Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Abstinence relative to heterosexual activity is acceptable if this is the established and preferred contraception for the subject.

PPD

\_\_\_\_\_  
Clinical Research Director or Designee  
(CAPITAL LETTERS)

PPD

\_\_\_\_\_  
Signature

14-AUG-2015

\_\_\_\_\_  
Date

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Principal Investigator  
(CAPITAL LETTERS)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date