Official Protocol Title:	A Phase III, Multicenter, Randomized, Double-Blind, Active-Comparator-Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Ertugliflozin (MK-8835/PF-04971729) Compared With the Addition of Glimepiride in Subjects With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin
NCT number:	NCT01999218
Document Date:	26-Feb-2015

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

SPONSOR:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

Ertugliflozin (MK-8835/PF-04971729) is being co-developed by Merck and Pfizer.
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. is the regulatory Sponsor of this study.

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder.

TITLE:

A Phase III, Multicenter, Randomized, Double-Blind, Active-Comparator-Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Ertugliflozin (MK-8835/PF-04971729) Compared With the Addition of Glimepiride in Subjects With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin

IND NUMBER: 106,447

EudraCT NUMBER: 2013-003582-34

Merck Protocol Number: 002-01

Pfizer Protocol Number: B1521013

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change	Rationale
4.2.2	Rationale for Dose Selection/Regimen	Reference to 'tablets' was removed to clarify that this refers to dose strength and not to whether subject receives tablet or capsule.	The source for glimepiride/matching placebo will change. The original glimepiride/matching placebo supplies were provided as tablets but will be switched to capsules.
5.2 5.2.1.2	Trial Treatments Dose Modification of Glimepiride/Matching Placebo for Glimepiride	Text was revised to indicate that subjects will initially be taking glimepiride tablets or matching placebo tablets but will be switched to glimepiride capsules or matching placebo capsules.	As above
7.1.5 8.2.9 9.1 12.4	Visit Requirements Compliance (Medication Adherence) Investigational Product Glimepiride Dosing Instructions	The text 'or capsules' was added.	As above

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.1.2.2	Safety Information for Ertugliflozin and Other SGLT2 Inhibitor Agents	Text revised to include all currently approved SGLT2 inhibitors in US and EU.	Updated to include other compounds in this class approved since initial protocol approval.
4.2.3.1	Efficacy Endpoints	The text 'changes from baseline at Week 52 and 104 for' added.	Text added to clarify when the efficacy endpoint will be analyzed.
5.2	Trial Treatments	Text updated to indicate that open-label sitagliptin rescue medication may be sourced centrally by the Sponsor.	The open-label sitagliptin rescue medication sourcing strategy was changed in the United States.
5.2.3	Trial Blinding/Masking	Text modified to clarify that ertugliflozin and glimepiride will be packaged identically relative to their matching placebos so that the blind/masking is maintained.	Text added for clarity.

5.8	Subject Withdrawal/Discontinuation Criteria	The 'Note' associated with the 'Parameters of Renal Function' discontinuation criterion was updated.	The update provides guidance of when repeat serum creatinine/eGFR measurements should be performed (i.e., within 7 days) after discontinuation thresholds for these parameters are initially met and when discontinuation of drug should occur.
5.8 12.5	Subject Withdrawal/Discontinuation Criteria Management of Subjects with Elevated Liver Enzymes	The text 'or longer' added to discontinuation criterion #4.	Text added to clarify circumstances subjects may qualify for discontinuation based on ALT or AST elevations.
6.0	Study Flow Chart	The text 'in Duplicate' or 'in Triplicate' was added to weight, vitals and Postural (Orthostatic) Blood Pressure and Pulse Rate procedure descriptions.	Text added for consistency with sections describing procedures for collecting vital signs (section 7.1.2.2), body weight (section 7.1.2.4), and postural blood pressure (section 7.1.2.3).
6.0	Study Flow Chart	The 'X' was removed from the 'Contact IVRS at Rescue Visit' row in the Study Flow Chart.	IVRS specifications do not require sites to call the IVRS at the rescue visit.

6.0	Study Flow Chart	Footnote ‘o’ regarding collection of C-peptide/proinsulin was removed from the A1C row at Rescue and Discontinuation Visit.	Footnote for C-peptide and proinsulin is not applicable to A1C.
6.0	Study Flow Chart	The text ‘Oxford’ removed from Contact IVRS at Discontinuation Visit.	Typographical error corrected.
7.1.1.8.8	Medication Compliance Monitoring	The text ‘Blinded investigational product but will’ removed.	Typographical error corrected.
7.1.2.4	Body Weight	The text ‘approximately’ added.	Text added to clarify that the accuracy checks of scales are required approximately monthly.
7.1.3	Laboratory Procedures/Assessments	The text ‘C-peptide’ added to lists of laboratory tests masked from Visit 4/Randomization to the end of the study.	C-peptide masking was added to central laboratory specification; protocol modified to match specifications.
7.1.3.1	Laboratory Evaluations (Hematology, Chemistry, Urinalysis and Others)	Specified that ‘Routine’ laboratory safety tests required at least a 10-hour fast.	Text added for clarity.

7.1.4.2	Blinding/Unblinding	Duplicate sentence 'IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.' removed.	Typographical error corrected.
7.3.4	Clinical Adjudication Committee	Venous thromboembolic events and hospitalized heart failure incorporated into the paragraph summarizing the rationale for adjudication of cardiovascular (CV) events.	The list of CV events for adjudication includes venous thromboembolic and hospitalized heart failure events; summary paragraph updated for consistency.
8.1.1 8.2.3.1 8.2.7	Efficacy Analysis Statistical Methods for Efficacy Analyses Subgroup Analyses and Effect of Baseline Factors	Added 'baseline eGFR' into the analysis models.	The level of renal function may impact efficacy because ertugliflozin has a renal-based mechanism.
8.1.1	Efficacy Analysis	Removed sentence saying that superiority for A1C will be declared if the upper bound of the 95% confidence interval excludes 0.	Details regarding the evaluation of superiority for A1C have been moved to Sections 8.1.3, 8.2.3.1, and 8.2.5.

8.1.3 and 8.2.5	Multiplicity	• Revised the multiplicity schema to require success in the test of A1C for the 5 mg dose before testing other endpoints for the 5 mg dose while controlling the type 1 error rate at < 0.05. • Added an evaluation of superiority for A1C	• Requested by regulatory agencies. • Allow an evaluation of superiority that preserves the overall type 1 error.
8.2	Statistical Analysis Plan	Changed 'protocol violators' to 'protocol deviators'	Consistency with other studies in the ertugliflozin program.
8.2.1.1	Efficacy Endpoints	• Changed endpoint from 'proportion of subjects with A1C ≤6.5' to 'proportion of subjects with A1C <6.5'. • Clarified that hypoglycemia is a safety endpoint	• Consistency with other studies in the ertugliflozin program. • Clarification
8.2.1.3	Derivation of Efficacy Endpoints	Clarified that composite endpoints must be computed based on samples collected on the same day.	Clarifications on analysis endpoints.
8.2.2	Analysis Populations	Added the analysis populations for summary tables of disposition and baseline characteristics.	Clarifications on analysis populations.

8.2.2.1	Efficacy Analysis Populations	Removed the '≥12 consecutive week' component of the Per-protocol population exclusion criterion related to incorrect study medication or change in metformin dose. Changed nomenclature from 'violation' to 'deviation' in the text describing PP population.	Consistency with other studies in the ertugliflozin program.
8.2.3	Statistical Methods	Stipulated that confirmed, adjudicated CV endpoints will be summarized in a separate report.	These results will be kept out of the CSR to preserve the integrity of the program-wide CV assessment.
8.2.3.1	Statistical Methods for Efficacy Analyses	• Set any eGFR values above 120 to be 120 in the analysis. • Added a section for sensitivity analyses to address the impact of missing data. • Revised text regarding the evaluation of superiority for A1C	• eGFR calculation can be unreliable at high values. • Sensitivity analyses to address different missing data mechanisms have been requested by regulatory agencies. • Allow an evaluation of superiority that preserves the overall type 1 error.

8.2.3.2	Statistical Methods for Safety Analyses	Clarified that data after the end of Treatment Period will be summarized separately. Clarified that the primary approach for analysis of hypoglycemia will exclude post-rescue data. Clarified the safety analyses in Table 12, and added a row for hypoglycemia. Clarified that including/ excluding rescue analysis approaches are not relevant for analyses of Phase B data alone. Clarified that the Tier 1 analysis of hypoglycemia will be used to address the objectives/hypotheses related to hypoglycemia	Clarifications on statistical methods.
8.2.9	Compliance (Medication Adherence)	Changed ‘tablets’ to ‘tablets or capsules’.	Accommodate the change in the source of glimepiride/ matching placebo in the compliance computation.

9.6	Standard Policies	Text related to the letter investigators send after unblinding to subjects who took exact match placebo was updated to include 'tablets' and to indicate patients who receive exact match placebo during placebo run-in will also be notified by letter.	Clarified language and intent of letter.
11.0	List of References	Added volume number and corrected page numbers to Reference #3.	Reference #3 was corrected.
12.2	Collection and Management of Specimens for Future Biomedical Research	The text 'legal guardians' as option to sign informed consent for specimens (i.e., DNA, RNA, protein, etc.) removed.	Legal guardians are not allowed to sign informed consents for this study.
12.5	Management of Subjects with Elevated Liver Enzymes	Numbering and bullets added to instructions.	Numbering and bullets added for improved readability.
12.7	Mapping of Relative Day Ranges to Weeks	Added logic for endpoints not collected at every visit.	Clarification of data handling methods.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-8835/PF-04971729 vs. Glimepiride in T2DM Subjects on Metformin
Trial Phase	Phase III
Clinical Indication	Treatment of Type 2 Diabetes Mellitus (T2DM)
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	ertugliflozin 5 mg q.d., ertugliflozin 15 mg q.d. or glimepiride up to 6 or 8 mg q.d. according to the local country label
Number of trial subjects	Approximately 1230 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 171 weeks from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for up to approximately 122 weeks from the time the subject signs the informed consent form (ICF) through the final contact. This will include a 1-week screening period (Visit 1 to Visit 2); an up to 13-week wash-off/titration/dose stabilization period (Visit 2 to Visit 3); a 2-week single-blind placebo run-in period (Visit 3 to Visit 4); a 104-week double-blind, active-comparator-controlled treatment period (Phase A – Year 1 [Visit 4 to Visit 10] followed by Phase B – Year 2 [Visit 10 to Visit 14]); telephone contacts at Weeks 3, 9, 32 and 45 and a post-treatment telephone contact 14 days after the last dose of blinded investigational product.
Randomization Ratio	1:1:1

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, randomized, double-blind, active-comparator-controlled parallel-group clinical trial of ertugliflozin (MK-8835/PF-04971729) in subjects with type 2 diabetes mellitus (T2DM) and inadequate glycemic control on metformin monotherapy. This trial will be conducted in conformance with Good Clinical Practices (GCP).

The duration of the trial will be up to approximately 122 weeks (with 14 scheduled clinic visits) for each subject. This will include a 1-week screening period (Visit 1 to Visit 2); an up to 13-week wash-off/titration/dose stabilization period (Visit 2 to Visit 3); a 2-week single-blind placebo run-in period (Visit 3 to Visit 4); a 104-week double-blind, active-comparator-controlled treatment period (Phase A – Year 1 [Visit 4 to Visit 10] followed by Phase B – Year 2 [Visit 10 to Visit 14]); telephone contacts at Weeks 3, 9, 32 and 45 and a post-treatment telephone contact 14 days after the last dose of blinded investigational product.

Approximately 1230 men and women ≥18 years of age with T2DM, diagnosed in accordance with American Diabetes Association (ADA) guidelines [1] with inadequate glycemic control (hemoglobin A_{1c} [A1C] ≥7.0% and ≤9.0% [≥53 mmol/mol and ≤75 mmol/mol]) while on a stable dose of metformin monotherapy (≥1500 mg/day for ≥8 weeks) and who meet all other enrollment criteria will be randomized.

Management of Subjects Prior to Randomization

Subjects who are on metformin monotherapy ≥1500 mg/day for ≥8 weeks with a Visit 1/Screening A1C ≥7.0% and ≤9.0% (≥53 mmol/mol and ≤75 mmol/mol) and who meet all other enrollment criteria will directly enter the 2-week, single-blind, placebo run-in period at a combined Visit 2/3.

Subjects who do not meet the above criteria but who are within one of the following three categories at Visit 1/Screening will be eligible to enter a variable wash-off/titration/dose stabilization period beginning at Visit 2 and will be scheduled for Visit 3/Week -2 according to Table 1.

on metformin monotherapy ≥1500 mg/day for <8 weeks with an A1C ≥7.0% and ≤9.0% (≥53 mmol/mol and ≤75 mmol/mol), or

on metformin monotherapy <1500 mg/day with an A1C ≥7.5% and ≤9.5% (≥58 mmol/mol and ≤80 mmol/mol), or

on metformin (any dose) in combination with a single allowable antihyperglycemic agent (AHA), including sulfonylureas (SUs) at <50% the maximum approved dose in the local country label, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, or alpha-glucosidase inhibitors (AGIs), with an A1C ≥6.5% and ≤8.5% (≥48 mmol/mol and ≤69 mmol/mol).

Table 1 Guidelines for Run-in Management

Regimen at Visit 1/Screening	A1C Entry Criterion at Visit 1/Screening	Subject Management Prior to Visit 3/Week -2
metformin ≥1500 mg/day for ≥8 weeks	≥7.0% and ≤9.0% (≥53 and ≤75 mmol/mol)	• Maintain metformin dose ≥1500 mg/day. • Go directly to a combined Visit 2/3.
metformin ≥1500 mg/day for <8 weeks	≥7.0% and ≤9.0% (≥53 and ≤75 mmol/mol)	• Maintain metformin dose ≥1500 mg/day for ≥8 weeks. • Go to Visit 3/Week -2.
metformin <1500 mg/day	≥7.5% and ≤9.5% (≥58 and ≤80 mmol/mol)	• Titrate metformin to ≥1500 mg/day. • Maintain metformin dose ≥1500 mg/day for ≥8 weeks. • Go to Visit 3/Week -2.
metformin (any dose) in combination with a single allowable AHA[1]	≥6.5% and ≤8.5% (≥48 and ≤69 mmol/mol)	• Discontinue non-metformin AHA. • Titrate metformin to ≥1500 mg/day (if necessary). • Maintain metformin dose ≥1500 mg/day for ≥8 weeks (≥10 weeks for subjects discontinuing SU therapy). • Go to Visit 3/Week -2.

[1]Allowable AHAs include: SUs at <50% the maximum approved dose in the local country label, DPP-4 inhibitors, meglitinides, and AGIs.

Subjects on a stable dose of metformin (≥1500 mg/day for ≥8 weeks or ≥10 weeks for those who discontinue SU therapy) with an A1C ≥7.0% and ≤9.0% (≥53 mmol/mol and ≤75 mmol/mol) at Visit 3/Week -2 and who meet all other enrollment criteria will be eligible to enter the double-blind treatment period beginning at Visit 4/Randomization (Day 1) after completing the 2-week single-blind placebo run-in period (Visit 3/Week -2 to Visit 4/Randomization [Day 1]).

Management of Randomized Subjects

At Visit 4/Randomization (Day 1), subjects will enter the 104-week, double-blind, active-comparator-controlled treatment period and be randomized in a 1:1:1 ratio to ertugliflozin 5 mg once-daily (q.d.), ertugliflozin 15 mg q.d., or glimepiride. Glimepiride/matching placebo will be initiated at 1 mg q.d. and titrated up to the maximum approved dose (6 or 8 mg q.d. based on the local country label) or maximum tolerated dose. Glimepiride/matching placebo may be down-titrated to avoid or manage hypoglycemia (see Section 5.2.1.2 for detailed instructions about titrating glimepiride). Subjects are to remain on their stable dose of metformin (≥1500 mg/day) while receiving blinded investigational product during the double-blind treatment period.

During Phase A/Year 1, subjects who are on the maximum labeled dose or maximum tolerated dose of glimepiride/matching placebo for at least two weeks and who meet progressively more stringent glycemic rescue criteria (see Table 6) will initiate open-label sitagliptin glycemic rescue medication in accordance with the local country label. Subjects who are rescued in Phase A/Year 1 will not be eligible to enter Phase B/Year 2. The study design does not include glycemic rescue therapy in Phase B/Year 2. During Phase B/Year 2, subjects who are on the maximum labeled dose or maximum tolerated dose of glimepiride/matching placebo for at least two weeks and who meet glycemic criteria specified in Section 5.8 will be discontinued from treatment with blinded investigational product.

Subjects who are discontinued from blinded investigational product for any reason other than withdrawal of consent will be followed by telephone contacts for the duration of the trial according to the Trial Flow Chart - Section 6.0. The purpose of these telephone contacts, as well as the 14-day post trial telephone contact, will be to collect SAEs and events eligible for adjudication (see Section 7.3.4).

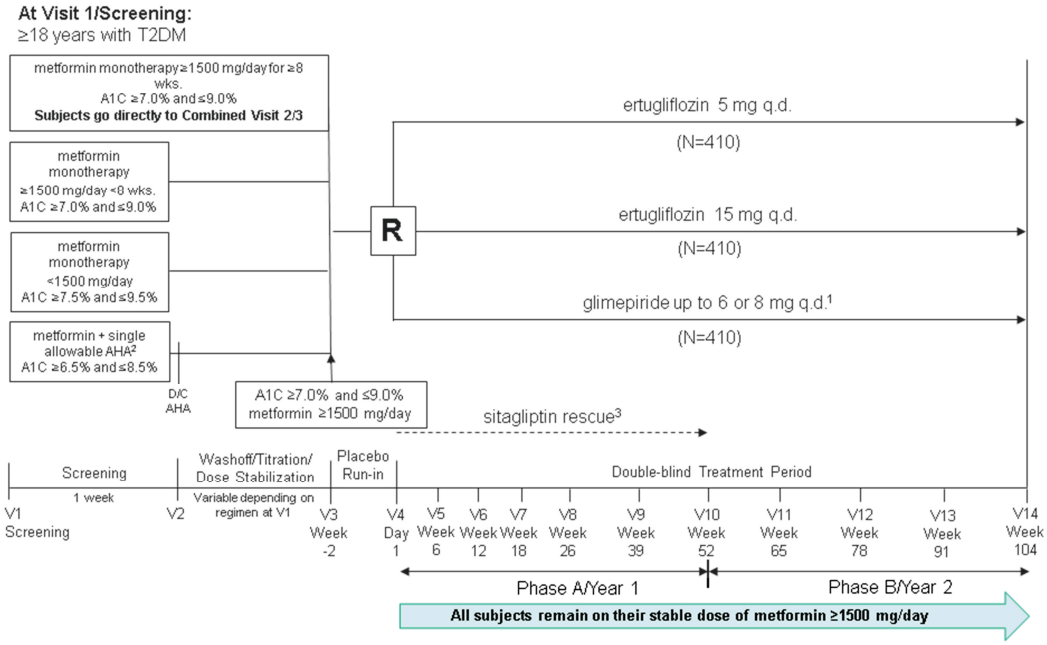
This trial is designed to evaluate, in adult subjects with T2DM and inadequate glycemic control on diet and exercise and metformin, the effect of both the 5 and 15 mg doses of ertugliflozin on glycemic control, symptomatic hypoglycemia, body weight, and blood pressure following a 52-week dosing period. It is also designed to evaluate the long-term efficacy, safety and tolerability of ertugliflozin during the entire 104-week double-blind, active-comparator-controlled treatment period.

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

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.



[1] based on maximum approved dose in the local country label
[2] allowable AHAs include: SUs at <50% the maximum approved dose in the local country label, DPP-4 inhibitors, meglitinides, or AGIs
[3] subjects rescued in Phase A/Year 1 will not be allowed to enter Phase B/Year 2; subjects will not be rescued in Phase B/Year 2
D/C = discontinue

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subjects with T2DM and inadequate glycemic control on metformin:

1) **Objective:** After 52 weeks, to assess the A1C-lowering efficacy of the addition of ertugliflozin 15 mg q.d. compared with the addition of glimepiride.

   Hypothesis: After 52 weeks, the change from baseline in A1C in subjects treated with the addition of ertugliflozin 15 mg q.d. is non-inferior compared with that in subjects treated with the addition of glimepiride.

2) **Objective:** To assess the safety and tolerability of ertugliflozin.

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with T2DM and inadequate glycemic control on metformin, after 52 weeks:

(1) **Objective:** To assess the effect of the addition of ertugliflozin 15 mg q.d. compared with the addition of glimepiride on the incidence of symptomatic hypoglycemia.

Hypothesis: The addition of ertugliflozin 15 mg q.d. leads to a lower incidence of symptomatic hypoglycemia compared with the addition of glimepiride.

(2) **Objective:** To assess the effect of the addition of ertugliflozin 15 mg q.d. compared with the addition of glimepiride on change in body weight from baseline.

Hypothesis: The addition of ertugliflozin 15 mg q.d. decreases body weight compared with the addition of glimepiride.

(3) **Objective:** To assess the A1C-lowering efficacy of the addition of ertugliflozin 5 mg q.d. compared with the addition of glimepiride.

Hypothesis: The change from baseline in A1C in subjects treated with ertugliflozin 5 mg q.d. is non-inferior compared with that in subjects treated with glimepiride.

(4) **Objective:** To assess the effect of the addition of ertugliflozin 5 mg q.d. compared with the addition of glimepiride on the incidence of symptomatic hypoglycemia.

Hypothesis: The addition of ertugliflozin 5 mg q.d. leads to a lower incidence of symptomatic hypoglycemia compared with the addition of glimepiride.

(5) **Objective:** To assess the effect of the addition of ertugliflozin 5 mg q.d. compared with the addition of glimepiride on change in body weight from baseline.

Hypothesis: The addition of ertugliflozin 5 mg q.d. decreases body weight compared with the addition of glimepiride.

(6) **Objective:** To assess the effect of the addition of ertugliflozin 15 mg q.d. compared with the addition of glimepiride on systolic blood pressure.

Hypothesis: The addition of ertugliflozin 15 mg q.d. reduces systolic blood pressure compared with the addition of glimepiride.

(7) **Objective:** To assess the effect of the addition of ertugliflozin 5 mg q.d. compared with the addition of glimepiride on systolic blood pressure.

Hypothesis: The addition of ertugliflozin 5 mg q.d. reduces systolic blood pressure compared with the addition of glimepiride.

The following objectives will be assessed for ertugliflozin 15 mg q.d. and 5 mg q.d.

In subjects with T2DM and inadequate glycemic control on metformin, after 52 weeks

(8) **Objective:** To assess the effect of the addition of ertugliflozin compared with the addition of glimepiride on change in fasting plasma glucose (FPG) from baseline.

(9) **Objective:** To assess the effect of the addition of ertugliflozin compared with the addition of glimepiride on the proportion of subjects at the A1C goal of <7.0% (<53 mmol/mol).

(10) **Objective:** To assess the effect of the addition of ertugliflozin compared with the addition of glimepiride on the proportion of subjects who require rescue and the time to rescue.

(11) **Objective:** To assess the effect of the addition of ertugliflozin compared with the addition of glimepiride on diastolic blood pressure.

(12) **Objective:** To assess the effect of the addition of ertugliflozin compared with the addition of glimepiride on durability of glycemic efficacy.

(13) **Objective:** To assess the effect of the addition of ertugliflozin compared with the addition of glimepiride on the proportion of subjects meeting the composite endpoint of an A1C decrease >0.5% with no symptomatic hypoglycemia and no body weight gain.

(14) **Objective:** To assess the effect of the addition of ertugliflozin compared with the addition of glimepiride on the proportion of subjects meeting the composite endpoint of an A1C <7.0% with no symptomatic hypoglycemia

(15) **Objective:** To assess the effect of the addition of ertugliflozin compared with the addition of glimepiride on lipid profile (including HDL-C, triglycerides, total cholesterol, LDL-C, and non-HDL-C cholesterol).

(16) **Objective:** To assess the effect of the addition of ertugliflozin compared with the addition of glimepiride on HOMA-%β.

In subjects with T2DM and inadequate glycemic control on metformin, after 104 weeks

(17) **Objective:** To assess the effects of the addition of ertugliflozin compared with the addition of glimepiride on A1C, FPG, and the proportion of subjects at the A1C goal of <7.0% (<53 mmol/mol).

(18) **Objective:** To assess the effects of the addition of ertugliflozin compared with the addition of glimepiride on symptomatic hypoglycemia.

(19) **Objective:** To assess the effects of the addition of ertugliflozin compared with the addition of glimepiride on change in body weight from baseline.

(20) **Objective:** To assess the effects of the addition of ertugliflozin compared with the addition of glimepiride on systolic and diastolic blood pressure.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-8835.

4.1.1 Pharmaceutical and Therapeutic Background

There has been an increase in the global prevalence of T2DM over the last several years, 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. Approximately 85% of patients with T2DM are obese or overweight, a key factor underlying the development and maintenance of insulin resistance [5, 6]. Individuals with T2DM have an increased risk of developing both microvascular and macrovascular disease associated 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 [7]. Orally administered pharmacological agents that lower glucose while also reducing other risk factors, e.g., by lowering body weight and reducing blood pressure, represent a major unmet medical need in the treatment of diabetes.

The sodium glucose co-transporter (SGLT) family (SLC5A) consists of 12 known members, including 6 gene products named SGLTs [8]. Sodium-Glucose co-Transporter 1 (SGLT1), a low capacity, high-affinity transporter with a sodium:glucose stoichiometry of 2:1, transports D-glucose as well as D-galactose and is primarily distributed in the intestine; it is also found in the S3 segment of the proximal tubule of the kidney where it is responsible for approximately 10% of glucose reabsorption. In contrast, Sodium-Glucose co-Transporter 2 (SGLT2) is primarily located in the S1/S2 segments of the proximal tubule of the kidney and is responsible for the reabsorption of approximately 90% of the glucose from the urine. SGLT2 utilizes a sodium ion gradient to actively transport glucose in a 1:1 stoichiometry and has been characterized as a high capacity, low affinity glucose transporter [9, 10, 11].

Ertugliflozin (MK-8835/PF-04971729) is a potent inhibitor of SGLT2 and possesses a high selectivity over glucose transport via SGLT1 and several other glucose transporters (GLUT1-4). Ertugliflozin inhibits renal glucose reabsorption resulting in urinary glucose excretion, thereby reducing plasma glucose and A1C in subjects with T2DM. Ertugliflozin is being developed as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

4.1.2 Clinical Trials

4.1.2.1 Efficacy of Ertugliflozin

In Phase II clinical studies, subjects received ertugliflozin for up to 12 weeks. Phase II results demonstrated that ertugliflozin significantly lowered A1C, blood pressure, and body weight without increasing the risk of hypoglycemia. In study B1521006 involving adult subjects with T2DM the following placebo-adjusted mean (80% CI) reductions in A1C (%) were observed for the 5 mg, 10 mg and 25 mg doses after 12 weeks of treatment: -0.69 (-0.89 to -0.49), -0.62 (-0.82 to -0.42) and -0.72 (-0.93 to -0.52) respectively. The placebo-adjusted mean (80% CI) reductions in body weight (%) for the 5 mg, 10 mg, and 25 mg doses were: -1.75 (-2.35 to -1.14), -2.15 (-2.76 to -1.54) and -1.91 (-2.52 to-1.30) respectively. The placebo-adjusted mean reductions in systolic blood pressure (mmHg) seen with doses of 5 mg, 10 mg and 25 mg were: -3.69 (-6.44 to -0.93), -2.77 (-5.59 to 0.05) and -2.77 (-5.56 to 0.02) respectively; and the placebo-adjusted mean reductions in diastolic blood pressure for the 5 mg, 10 mg and 25 mg doses were: -2.03 (-3.68 to -0.37), -4.12 (-5.81 to -2.42) and -2.40 (-4.08 to -0.73) respectively.

4.1.2.2 Safety Information for Ertugliflozin and Other SGLT2 Inhibitor Agents

Several SGLT2 inhibitors are in clinical development and as of February 2015, three SGLT2 inhibitors are approved in the U.S. and European Union (canagliflozin, dapagliflozin and empaglifozin). Based on available clinical trial data with dapagliflozin, canagliflozin and empagliflozin, several potential risks from SGLT2 inhibition have been identified. In clinical trials, the rate of genital fungal infections in males and females has consistently been higher in subjects receiving SGLT2 inhibitors as compared to placebo or other diabetes medications. Therefore, the increased risk of genital fungal infections can be considered a class effect of SGLT2 inhibitors. Glucosuria can potentially result in increased risk of urinary tract infection (UTI). In some clinical trials with SGLT2 inhibitors, the reported rate of UTI was slightly higher in subjects treated with a SGLT2 inhibitor compared to those receiving placebo.

SGLT2 inhibition leads to an increase in urinary excretion of glucose and sodium and a diuretic effect that is associated with an increase in urine output and a decrease in blood pressure similar to that reported with other agents with a diuretic action. In clinical trials with other SGLT2 inhibitors, this diuretic effect led to a slightly higher frequency of adverse events such as pollakiuria, thirst and polyuria, but these events were typically of mild severity and usually did not lead to discontinuation. However, certain populations of subjects (e.g., elderly or renally insufficient) may be at risk for hypovolemia-related adverse events from this mechanism. As SGLT2 inhibition can lead to volume depletion, there is also a potential concern for adverse renal effects. In subjects with moderate renal impairment, there was a slightly higher incidence of renal-related adverse events reported in subjects receiving SGLT2 inhibitors than controls in clinical trials with other SGLT2 inhibitors. Small initial decreases in the estimated glomerular filtration rate (eGFR) were seen, which returned toward baseline levels over time with continued treatment and/or upon discontinuation of therapy. The reversibility with continued treatment or with

discontinuation of treatment is consistent with a hemodynamic (plasma volume) mechanism. In patients with lower eGFR values at baseline, the percent decrease in eGFR was greater, but the pattern – an initial decline with a subsequent increase towards baseline – was similar to that in patients with more normal eGFR values.

Routine safety monitoring for these adverse events will be performed in this study.

The safety of ertugliflozin has been assessed in the clinical development program in healthy subjects as well as in subjects with T2DM. As of September 2013, a total of 479 subjects have been exposed to ertugliflozin in six completed Phase I and two completed Phase II studies. Oral doses of ertugliflozin as high as 300 mg (single dose), 100 mg once daily (up to 14 days), and 25 mg once daily (up to 12 weeks) were well tolerated with a safety profile supporting continued development.

As of September 2013, there have been no deaths, and a total of 11 serious adverse events (SAEs) were reported in 9 subjects. Across the program, a total of 10 subjects (1.5%) were withdrawn due to adverse events (AEs). The most frequent AEs reported with ertugliflozin use in the Phase I studies have been headache, constipation, diarrhea and nausea. In the two Phase II studies, upper respiratory, urinary tract and genital fungal infections, diarrhea, arthralgia and headache were most frequently reported. The incidences of these AEs however were low. Urinary tract infection was reported at a frequency of 3.3% for all ertugliflozin doses combined, versus 5.4% for placebo. The frequency of genital fungal infection was noted to be numerically higher in males and females receiving ertugliflozin treatment compared to placebo, and currently this AE is the only event considered to be an adverse drug reaction (ADR) for ertugliflozin. Overall, there was no clear dose-related increase in frequency of AEs with increasing dose of ertugliflozin.

In Phase II study B1521004, a mild diuretic effect was observed with ertugliflozin (i.e., increase in 24-hour urinary volume) though there was no dose-response relationship across the doses of ertugliflozin evaluated. In susceptible individuals, this diuretic effect from ertugliflozin could lead to volume depletion and related adverse events such as hypotension or dizziness, and these events will be monitored in the Phase III studies.

In Phase II, there were small increases observed in hemoglobin and hematocrit, suggestive of hemoconcentration, and a small increase in blood-urea-nitrogen (BUN) but no change in serum creatinine, at Week 12 relative to baseline. Given the small magnitude of the increases in BUN, and hemoglobin/hematocrit, these changes are unlikely to have clinical consequence. Small increases in mean serum phosphate, serum magnesium, and intact parathyroid hormone (iPTH) levels, all within the laboratory reference range, were observed following 12 weeks of dosing with ertugliflozin. There was a suggestion of changes in markers of bone resorption, though there did not appear to be a clear dose-dependent effect with increasing dose of ertugliflozin. In totality, the clinical relevance of these findings remains unclear. However, the effect of ertugliflozin on bone mineral density will be evaluated in a Phase III trial, and all clinical fractures reported in the Phase III program will be adjudicated by an independent committee and will be included in a pooled analysis.

In the clinical program to date, no clinically significant changes from baseline in serum aminotransferases (ALT and AST) have been observed.

Phase III clinical trial data from another SGLT2 inhibitor, dapagliflozin, revealed a numerical imbalance in the rates of breast and bladder cancer in dapagliflozin-treated subjects compared to control [12]. The causal relationship to dapagliflozin for this finding is uncertain given the small number of events, and the absence of any preclinical signal (no reported increase in either tumor in carcinogenicity studies) with dapagliflozin. Moreover, in the larger clinical program of another SGLT2 inhibitor, canagliflozin, no cancer imbalance, including in breast or bladder cancer events, was reported. Because thorough evaluation of malignancies is important in the development program of all investigational medications, detailed information will be collected for subjects who develop a malignancy. This information could include but is not limited to relevant medical history, biopsy, or operative reports, etc.

Complete information for this compound may be found in the Investigators' Brochure for ertugliflozin.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Metformin is the standard and preferred first-line pharmacological therapy for T2DM. However, T2DM is a progressive disease and with time many patients on metformin monotherapy require additional therapy to achieve glycemic goals. Combination therapy with metformin and an SU is a commonly used treatment regimen in subjects with T2DM. Although widely used, SUs are associated with the side effects of hypoglycemia and body weight gain. In the Phase II studies, subjects treated with ertugliflozin lost weight and hypoglycemia was reported infrequently. Since ertugliflozin improves glycemic control via a mechanism independent of insulin, it could potentially represent a viable therapy across the typical disease progression of T2DM, including individuals who have inadequate control on metformin therapy.

The present trial will assess the safety and efficacy of ertugliflozin compared with the SU, glimepiride, in subjects with T2DM and inadequate glycemic control on metformin monotherapy. Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent Forms (ICFs).

4.2.2 Rationale for Dose Selection/Regimen

The proposed ertugliflozin doses to be evaluated in Phase III are 5 mg and 15 mg once daily. Since oral doses of ertugliflozin as high as 300 mg (single dose), 100 mg once daily (up to 14 days) and 25 mg once daily (up to 12 weeks) were safe and well-tolerated, dose selection was based on dose-response modeling of efficacy end-points (A1C and FPG) from study B1521006 as well as 24-hour urinary glucose excretion (mechanism biomarker) in T2DM subjects from study B1521004. For these end-points, the 5 mg and 15 mg doses consistently elicit a response that is >80% and >90% of the maximum response, respectively (Table 2.)

Table 2 Estimated Percent Maximum Response for Various Endpoints

Ertugliflozin Dose	UGE – T2DM (ED_{50}=0.78 mg)	A1C (ED_{50}=1 mg)	FPG (ED_{50}=1.1 mg)
5 mg	87%	83%	82%
15 mg	95%	94%	93%
UGE = urinary glucose excretion; ED_{50} = dose producing half (50%) of the maximal response.			

In addition, the dose-response modeling of 24-hour UGE in healthy volunteers estimated the ED_{50} at 3 mg, which translates to 63% and 83% of maximum effect for 5-mg and 15-mg doses. The selection of the 5 mg and 15 mg doses is also supported by the safety and tolerability profile for ertugliflozin in clinical studies up to 12 weeks in duration. When accounting for species differences in protein binding, the highest Phase III dose of 15 mg once daily represents an exposure which is approximately 12-fold [for C_{max}] and 11-fold [for $AUC_{(0-24)}$] lower than exposure at the no observed adverse effect level (NOAEL) in the 6-month toxicology study in the most sensitive species (rat). Thus, both the 5 and 15 mg doses are expected to provide clinically meaningful efficacy and allow for a thorough assessment of the benefit/risk of ertugliflozin in the Phase III program.

Glimepiride is a commonly used SU agent, which some trials have suggested has a lower risk of hypoglycemia relative to other SU agents [13, 14]. The usual starting dose of glimepiride is 1 to 2 mg q.d. In order to reduce the risk of hypoglycemia, glimepiride will be initiated at 1 mg q.d. (for subjects randomized to this treatment group) and up-titrated as considered appropriate by the investigator based on the subject's glycemic response and risk of hypoglycemia, based on the guidance in Table 5 in Section 5.2.1.2.1. Glimepiride may be up-titrated to a maximum daily dose (6 or 8 mg q.d.) according to the maximum approved dose in the local country label) or to the subject's maximum tolerated dose. Investigators may have subjects take combinations of 1 or 2 mg strengths to achieve a dose the investigator considers appropriate (e.g., 3 mg, 5 mg).

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Glycemic efficacy endpoints will include changes from baseline at Week 52 and Week 104 for A1C and FPG. A1C reflects average glucose concentrations over the past 3-4 months and, therefore, provides a useful index of the glycemic control of ertugliflozin over that time period. It is a standard efficacy endpoint used to assess the glycemic efficacy of AHAs. A1C is a key glycemic parameter which correlates with reduction of risk of diabetic microvascular complications. The measurement of FPG will provide insight into the effects of ertugliflozin on FPG and characterize the earlier time course of glucose control in this trial.

Other efficacy endpoints that will be assessed include changes from baseline at Week 52 and 104 for body weight, systolic blood and diastolic blood pressure. Refer to Section 8.0 for further detail.

4.2.3.2 Safety Endpoints

Safety assessment will include collection of adverse events, a hypoglycemic assessment log to collect information on each potential episode of hypoglycemia (including concurrent fingerstick glucose value), physical examination including vital signs, and sitting and postural blood pressures. Laboratory safety studies will include blood chemistry, lipid panel, hematology, urinalysis, and urine pregnancy testing (performed in women of childbearing potential), and centrally-read electrocardiograms (ECGs). Refer to Section 8 for specific safety measurements collected during the study and for further details.

4.2.3.3 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

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

5.1.2 Subject Inclusion Criteria

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

At Visit 1/Screening

1. Have T2DM in accordance with ADA guidelines [1] and be ≥18 years of age on the day of signing the ICF.

2. Meet one of the following criteria:

   - On metformin monotherapy ≥1500 mg/day for ≥8 weeks with a Visit 1/Screening A1C ≥7.0% and ≤9.0% (≥53 mmol/mol and ≤75 mmol/mol)

   OR

   - On metformin monotherapy ≥1500 mg/day for <8 weeks with a Visit 1/Screening A1C ≥7.0% and ≤9.0% (≥53 mmol/mol and ≤75 mmol/mol)

   OR

- On metformin monotherapy <1500 mg/day with a Visit 1/Screening A1C ≥7.5% and ≤9.5% (≥58 mmol/mol and ≤80 mmol/mol)

OR

- On metformin in combination with a single allowable AHA (i.e., SUs at <50% the maximum approved dose in the local country label, DPP-4 inhibitors, meglitinides, or AGIs) with a Visit 1/Screening A1C ≥6.5% and ≤8.5% (≥48 mmol/mol and ≤69 mmol/mol)

3. Have a body mass index (BMI) ≥18.0 kg/m^2.

4. 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.

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

6. 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 ≥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 investigational product and for 14 days after the last dose of blinded investigational product. 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 an 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 3/Week -2

7. Be on metformin monotherapy (≥1500 mg/day) for ≥8 weeks (or ≥10 weeks for subjects who washed off SU) and have an A1C ≥7.0% and ≤9.0% (≥53 mmol/mol and ≤75 mmol/mol).

At Visit 4/Randomization/Day 1

8. Be ≥80% compliant with the 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 SGLT2 inhibitor.

4. Has been treated with any of the following agents within 12 weeks of Visit 1/Screening or during the pre-randomization period:

    - Insulin of any type (except for short-term [i.e., ≤7 days] use during hospitalization and no longer required)
    - Other injectable anti-hyperglycemic agents (AHA) [e.g., pramlintide, exenatide, liraglutide]
    - Pioglitazone or rosiglitazone
    - Other SGLT2 inhibitor
    - Bromocriptine (Cycloset™)
    - Colesevelam (Welchol™)
    - Any other AHA with the exception of the protocol-approved agents

5. Has a known hypersensitivity or intolerance to metformin or glimepiride.

6. Meets any of the following criteria:

    - Subject is on a weight-loss program and is not weight-stable.
    - Subject is on a weight-loss medication (e.g., orlistat, phentermine/topiramate, lorcaserin) and is not weight-stable.
    - Subject is on other medications associated with weight changes (e.g., anti-psychotic agents) and is not weight-stable.
    - Subject has undergone bariatric surgery >12 months prior to Visit 1/Screening and is not weight-stable.
    - Subject has undergone bariatric surgery within 12 months of Visit 1/Screening.

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

Concomitant Disease of Organs and Systems

7. 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.

8. Has active, obstructive uropathy or an indwelling urinary catheter.

9. Has a history of malignancy ≤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, or renal cell carcinoma is excluded.

10. Has human immunodeficiency virus (HIV) as assessed by medical history.

11. 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).

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

13. Has any clinically significant malabsorption condition.

14. Is currently being treated for hyperthyroidism.

15. 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.

Exclusion Criteria Based on Laboratory Abnormalities

16. Has an exclusionary laboratory value as listed in Table 3 below:

Table 3 Laboratory Exclusion Criteria

Parameter[1]	Population (if applicable)	Trial Limit for Exclusion
eGFR[2]		<55 mL/min/1.73 m^2
Serum creatinine	Male Female	≥1.3 mg/dL (115 μmol/L) ≥1.2 mg/dL (106 μmol/L)
Alanine aminotransferase (ALT)		>2 times Upper Limit of Normal (ULN)
Aspartate aminotransferase (AST)		>2 times ULN
Thyroid-stimulating hormone (TSH)[3]		Outside central laboratory normal range
Hemoglobin	Male Female	<12 g/dL (120 g/L) <11 g/dL (110 g/L)
Triglycerides (TG)[4]		>600 mg/dL (6.78 mmol/L)

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

Other Criteria

17. Has been previously randomized in a study with ertugliflozin.

18. 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.

19. Has undergone a surgical procedure within 6 weeks prior to signing the ICF or has major surgery planned during the trial.

    Note: A subject who has undergone minor surgery within the 6 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.

20. Has a positive urine pregnancy test.

21. Is pregnant or breast-feeding, or is planning to conceive during the trial, including 14 days following the last dose of blinded investigational product.

22. Is planning to undergo hormonal therapy in preparation to donate eggs during the trial, including 14 days following the last dose of blinded investigational product.

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

24. 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.

25. 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.

26. Has a mean value for triplicate sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg (after at least a 5-minute seated rest) and blood pressure is considered unlikely to be below these limits by Visit 4/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 4/Randomization (Day 1). Subjects who have blood pressure medication initiated or adjusted *cannot* have a combined Visit 2/3. Subjects on blood pressure medication must be on a stable regimen for at least 4 weeks prior to Visit 4/Randomization (Day 1).

27. Is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial.

At Visit 3/Week -2

28. Has a clinically significant ECG abnormality that requires further diagnostic evaluation or intervention (e.g., new, clinically significant arrhythmia or a conduction disturbance).

29. Is on or likely to require treatment for ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids.

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

30. Has a FPG consistently (i.e., measurement repeated and confirmed within 7 days) >260 mg/dL (14.4 mmol/L).

31. Has a positive urine pregnancy test.

32. 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 require evaluation of TG levels at Visit 3/Week -2 to assess eligibility following initiation or adjustment of lipid-lowering medication.

At Visit 4/Randomization (Day 1)

33. Has a site fasting fingerstick glucose (FFSG) <126 mg/dL (7.0 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 3/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 4/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 4/Randomization (Day 1), the subject MUST be excluded.

34. Has a positive urine pregnancy test.

35. Is on lipid-lowering medication, blood pressure medication, or thyroid replacement therapy and *has not* been on a stable regimen for the 4 weeks (lipid-lowering medication and blood pressure medication) or 6 weeks (thyroid replacement therapy) prior to Visit 4/Randomization (Day 1).

    Note: The current visit can be changed to an Unscheduled Visit, and the subject should be rescheduled for a Visit 4/Randomization (Day 1). Additional single-blind placebo run-in medication should be dispensed if needed.

36. Has a mean value for triplicate 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).

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

5.2 Trial Treatment(s)

Treatments to be used in this trial are outlined below in Table 4.

Table 4 Trial Treatments

Treatment Group	Drug/Dose	Use	Dose Frequency/ Treatment Period	Route of Administration
placebo run-in (all groups)	matching placebo for ertugliflozin 5 mg	placebo (trial drug)	q.d. for 2 weeks	oral
	matching placebo for ertugliflozin 10 mg			
	matching placebo for glimepiride 1 mg	placebo (active-comparator)		
ertugliflozin 5 mg group	ertugliflozin 5 mg	investigational (trial drug)	q.d. for 104 weeks	oral
	matching placebo for ertugliflozin 10 mg	placebo (trial drug)		
	matching placebo for glimepiride 1 mg	placebo (active-comparator)		
	matching placebo for glimepiride 2 mg			
ertugliflozin 15 mg group	ertugliflozin 5 mg	investigational (trial drug)	q.d. for 104 weeks	oral
	ertugliflozin 10 mg			
	matching placebo for glimepiride 1 mg	placebo (active-comparator)		
	matching placebo for glimepiride 2 mg			

Treatment Group	Drug/Dose	Use	Dose Frequency/ Treatment Period	Route of Administration
glimepiride group	glimepiride 1 mg	active-comparator	q.d. for 104 weeks	oral
	glimepiride 2 mg			
	matching placebo for ertugliflozin 5 mg	placebo (trial drug)		
	matching placebo for ertugliflozin 10 mg			
sitagliptin rescue medication	open-label sitagliptin according to local country label	rescue medication	q.d. as required	oral

The first doses of single-blind matching placebo for ertugliflozin and matching placebo for glimepiride will be administered at the trial site as witnessed doses at Visit 3/Week -2 or combined Visit 2/3. The first doses of double-blind ertugliflozin/matching placebo and glimepiride/matching placebo will be administered at the trial site as witnessed doses at Visit 4/Randomization (Day 1). 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 will be the responsibility of the subject throughout the duration of the trial.

Ertugliflozin (5 and 10 mg) and matching placebos will be administered in a blinded manner as oral tablets q.d. Glimepiride (1 and 2 mg) and matching placebos will be administered in a blinded manner as oral tablets q.d. and will be switched to oral capsules q.d. Subjects randomized to ertugliflozin 5 mg q.d. will take one ertugliflozin 5 mg tablet, one matching placebo tablet for ertugliflozin 10 mg, and matching placebo(s) for glimepiride daily. Subjects randomized to ertugliflozin 15 mg q.d. will take one 5 mg tablet and one 10 mg tablet and matching placebo(s) for glimepiride daily. Subjects randomized to glimepiride will take matching placebo tablets for ertugliflozin 5 mg and 10 mg daily and will take glimepiride tablets (1 and/or 2 mg) but will then be switched to glimepiride capsules (1 and/or 2 mg).

Open-label sitagliptin rescue medication will be sourced centrally by the Sponsor or locally sourced by the subsidiary or designee, investigator site or by prescription. The trial investigator will be responsible for managing the initiation and maintenance of rescue medication in accordance to the local country label.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

5.2.1.2 Dose Modification of Glimepiride/Matching Placebo for Glimepiride

The dose of glimepiride/matching placebo may be up- and/or down-titrated at a scheduled or unscheduled visit or by telephone contact throughout the 104-week double-blind treatment period based on fingerstick glucose determinations performed in the clinic or at home and by the investigator's clinical assessment of the subject's glycemic status (based on the guidance in Table 5). At Weeks 3, 9, 32 and 45, site personnel will contact subjects by telephone to review their glycemic status and glimepiride titration may be recommended accordingly. Glycemic status will also be reviewed at clinic visits. A Glimepiride Dosing Instructions log, an optional tool to help sites instruct subjects how to take glimepiride/matching placebo during the double-blind treatment period (Visit 4/Randomization/Day 1 to Visit 14/Week 104), is provided in Section 12.4 and may be reviewed with patients at clinic visits or during telephone contacts. Glimepiride will be initially supplied as 1-mg and 2-mg tablets and switched to 1-mg and 2-mg capsules.

5.2.1.2.1 Up-Titration of Glimepiride/Matching Placebo for Glimepiride

At Visit 4/Randomization (Day 1), glimepiride/matching placebo will be initiated at 1 mg q.d. At Week 3, the investigator will contact the subject by telephone to review their self-monitored blood glucose (SMBG) results and to perform a clinical assessment of the subject's glycemic status. If considered appropriate by the investigator (based on the guidance in Table 5), the glimepiride/matching placebo will be up-titrated to 2 mg/day (2 x 1 mg tablet). At Visit 5/Week 6, subjects on 2 x 1 mg tablet per day will be switched to 2 mg tablets, while subjects on 1 mg q.d. will continue on the 1 mg tablets. After Visit 5/Week 6, up-titration will occur if a subject meets all requirements for up-titration in Table 5.

Table 5 Guidance for Up-Titration of Glimepiride

1.	FFSG at the clinic or most recent SMBG is ≥110 mg/dL (6.1 mmol/L)
2.	Fasting (on at least 2 occasions) and pre-prandial fingerstick glucoses are all ≥110 mg/dL (6.1 mmol/L) during the week prior to up-titration
3	No hypoglycemic episodes have occurred since the prior up-titration, if applicable
4.	Investigator believes that further up-titration would not place the subject at risk for hypoglycemia

Although the initial portion of the double-blind treatment period is designed with 3-week intervals between subject contacts (via telephone calls and a clinic visit) to support up-titration of glimepiride/matching placebo, up-titration may also occur at any time during the double-blind treatment period by telephone calls or at scheduled or unscheduled visits. The frequency of the up-titration(s) is at the discretion of the investigator; however, the interval between each up-titration should be at least one week. Investigators may have subjects take combinations of 1- and 2-mg strengths to achieve doses the investigator considers appropriate (e.g., 3 mg, 5 mg).

5.2.1.2.2 Down-titration of Glimepiride/Matching placebo for Glimepiride

If a subject experiences unexplained hypoglycemia (i.e., not explained by missed meals or excess physical activity) or explained hypoglycemia with the precipitating events likely to continue or reoccur, the subject's glimepiride/matching placebo should be down-titrated as determined appropriate by the investigator. If the subject continues to experience hypoglycemia after glimepiride/matching placebo has been down-titrated to 1 mg q.d. or if the subject was on 1 mg q.d. at the time of the initial episodes of hypoglycemia, therapy with glimepiride/matching placebo should be interrupted. Subjects experiencing hypoglycemia may continue in the trial off glimepiride/matching placebo. If hypoglycemia continues to occur after glimepiride/matching placebo is interrupted, the subject should be considered for discontinuation from the blinded investigational product according to Section 5.8 – Subject Withdrawal/Discontinuation Criteria.

If a subject has had glimepiride/matching placebo interrupted or down-titrated, and re-initiation and/or up-titration of therapy is considered appropriate, then re-initiation and/or up-titration of glimepiride/matching placebo may be performed according to the guidelines used for initial up-titration.

Note: Subjects rescued with sitagliptin who experience hypoglycemia must first interrupt sitagliptin and if the subject continues to have hypoglycemia, the dose of glimepiride/matching placebo should be down-titrated and if necessary interrupted/discontinued as described above.

5.2.1.3 Dose Modification of Ertugliflozin/Matching Placebo for Ertugliflozin

The dose of ertugliflozin (5 or 15 mg q.d.) or matching placebo for ertugliflozin cannot be modified throughout the 104-week double-blind treatment period.

5.2.1.4 Dose Modification of Metformin

The dose of metformin (≥1500 mg/day) should remain stable throughout the 104-week double-blind treatment period.

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

5.2.2 Timing of Dose Administration

At Visit 4/Randomization (Day 1), each subject will be randomly assigned to ertugliflozin 5 mg q.d., ertugliflozin 15 mg q.d. or glimepiride. Subjects will be instructed to take double-blind investigational product (ertugliflozin, glimepiride and matching placebos) orally at approximately the same time of day in the morning from Visit 4/Randomization (Day 1) through Visit 14/Week 104 or early discontinuation. Subjects will be instructed not to take double-blind investigational product the morning of the clinic visit.

If a subject misses a dose of blinded investigational product 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. Ertugliflozin and glimepiride 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

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are three treatment arms. Subjects will be assigned randomly in an 1:1:1 ratio to ertugliflozin 5 mg q.d., ertugliflozin 15 mg q.d., or glimepiride.

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.

Prohibited Medications

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

1. Other Antihyperglycemic Medications:
    - Insulin of any type (except for short-term use during hospitalization and no longer required)
    - Other injectable AHAs [e.g., pramlintide, exenatide, liraglutide]
    - Pioglitazone or rosiglitazone
    - SGLT2 inhibitors (except blinded ertugliflozin)
    - SUs (except blinded glimepiride)
    - DPP4 inhibitors (except sitagliptin rescue medication)
    - Bromocriptine (Cycloset™)
    - Colesevelam (Welchol™)
    - Any other AHA with the exception of the protocol-approved agents
2. Corticosteroids: Treatment for ≥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.

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 4/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 4/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 investigational product during the double-blind treatment period and for 14 days after the last dose of blinded investigational product.

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 3 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 3/Week -2 or combined Visit 2/3 should be instructed not to change the use or dose of the supplement during the trial. Subjects should be instructed not to initiate new supplements during the trial.

5.6 Rescue Medications & Supportive Care

During Phase A/Year 1, subjects who are on the maximum labeled dose (6 or 8 mg q.d.) or maximum tolerated dose (if lower than maximum dose) of glimepiride/matching placebo for at least two weeks and who meet progressively more stringent glycemic rescue criteria (see Table 6) will receive open-label sitagliptin glycemic rescue medication. Sitagliptin must be initiated at either a scheduled or unscheduled visit at the investigational site, and not by a telephone contact. Immediately prior to initiation of rescue medication (at a scheduled or unscheduled visit), subjects meeting rescue criteria must undergo the Rescue Visit procedures referenced in the Trial Flow Chart - Section 6.0. Do NOT collect A1C if the rescue visit occurs within six weeks after Visit 4/Randomization (Day 1). Subjects rescued during Phase A/Year 1 will not be eligible to enter Phase B/Year 2. During Phase B/Year 2, subjects who are on the maximum labeled dose or maximum tolerated dose of glimepiride/matching placebo for at least two weeks and who have FPG results consistently >200 mg/dL (11.1 mmol/L) or A1C >8.0% (64 mmol/mol) will be discontinued from blinded investigational product (see Section 5.8).

The dose of sitagliptin should be initiated according to the local country label. Subjects who have a prior history of hypersensitivity or intolerance to sitagliptin will be discontinued from blinded investigational product (see Section 5.8).

Subjects requiring sitagliptin rescue medication will continue to receive blinded investigational product.

Table 6 Phase A/Year 1 Glycemic Thresholds

Visit Interval	Glycemic Threshold
After Visit 4/Randomization (Day 1) through Visit 5/Week 6:	FPG consistently >270 mg/dL (15.0 mmol/L)
After Visit 5/Week 6 through Visit 6/Week 12:	FPG consistently >240 mg/dL (13.3 mmol/L)
After Visit 6/Week 12 through Visit 8/Week 26:	FPG consistently >200 mg/dL (11.1 mmol/L)
After Visit 8/Week 26:	FPG consistently >200 mg/dL (11.1 mmol/L) or A1C >8.0% (64 mmol/mol)
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.	

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

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

5.7.1.1 Alcohol, Caffeine and Tobacco

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

5.7.2 Activity

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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 new agent in development, including ertugliflozin, **the investigator should determine if a subject who no longer agrees to *actively* participate (i.e., no longer attend visits at the investigational site, take blinded investigational product, and have other study-related procedures conducted at the investigational site) is agreeable to providing additional *follow-up information* through interval telephone contacts** (with the site collecting only important health status information (e.g., SAEs and events eligible for adjudication [see Section 7.3.4]). See Section 5.8.1 for additional details about monitoring subjects who discontinue treatment with blinded investigational product.

A subject must be discontinued from blinded investigational product (but may continue to be monitored in the trial) for the following reasons:

1. Subject was rescued with sitagliptin during Phase A/Year 1 and completed Phase A/Year 1.
2. Subject meets protocol-specified hyperglycemia criteria, as specified below:

   Phase A/Year 1: 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) despite receiving a maximum labeled or maximum tolerated (if lower than maximum labeled) dose of glimepiride/matching placebo for at least two weeks and glycemic rescue therapy with sitagliptin for at least 4 weeks:

   - FPG consistently >270 mg/dL (15.0 mmol/L) after Visit 4/Day 1 through Visit 5/ Week 6.
   - FPG consistently >240 mg/dL (13.3 mmol/L) after Visit 5/Week 6 through Visit 6/ Week 12.
   - FPG consistently >200 mg/dL (11.1 mmol/L) after Visit 6/Week 12 through Visit 8/Week 26.
   - FPG consistently >200 mg/dL (11.1 mmol/L) or A1C >8.0% (64 mmol/mol) after Visit 8/Week 26

   Phase B/Year 2: Subjects who have a repeated, confirmed FPG >200 mg/dL (11.1 mmol/L) or single A1C >8.0% without a reasonable explanation (e.g., intercurrent illness or medication omission) despite receiving a maximum labeled or maximum tolerated (if lower than maximum labeled) dose of glimepiride/matching placebo for at least two weeks.

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

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

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

   Note: Subjects should only be discontinued from blinded investigational product due to hypoglycemia after the subject has down-titrated and interrupted glimepiride/matching placebo (see Section 5.2.1.2.2). Subjects rescued with sitagliptin must first interrupt sitagliptin and if the subject continues to experience hypoglycemia, the dose of glimepiride/matching placebo should be down-titrated and if necessary interrupted. If the subject continues to experience hypoglycemia despite interruption of glimepiride/matching placebo, all blinded investigational product should be discontinued.

4. Abnormal liver function tests meeting criteria specified below (see Section 12.5 for additional details on management and discontinuation of blinded investigational product for subjects with elevated liver enzymes).

    - ALT or AST ≥3X ULN with total bilirubin (TBL) ≥2X ULN and alkaline phosphatase (ALP) <2X ULN and without an established etiology; or
    - ALT or AST ≥8X ULN or ≥3X ULN with symptoms consistent with liver injury and without an established etiology; or
    - ALT or AST ≥5X ULN for 2 weeks or longer; or
    - ALT or AST ≥3X ULN and subject is unwilling or unable to undergo repeat ALT and AST testing at the frequency defined in Section 12.5.

5. Parameters of Renal Function:

    Serum creatinine concentrations consistently ≥1.5 mg/dL (133 μmol/L) in men or ≥1.4 mg/dL (124 μmol/L) in women.

    OR

    eGFR consistently <45 mL/min/1.73 m^2 (MDRD formula).

    Note: A consistent value is defined as a repeat measurement performed within 7 days of notification from the central laboratory. If the eGFR or serum creatinine value continues to meet discontinuation criteria but demonstrates stability or improvement relative to the prior result, an additional repeat may be performed (within 7 days). If this repeat continues to meet the discontinuation criteria, the subject must be discontinued. See Section 7.1.5.9 for guidance on following subjects who discontinue blinded investigational product due to decreased renal function or renal-related adverse events.

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

7. Subjects have been rescued or who meet the threshold for glycemic rescue medication and have a known hypersensitivity or intolerance to sitagliptin.

8. Pregnancy

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

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

10. The investigator or subject becomes unblinded to the subject's treatment assignment.

The Sponsor or its delegate should be immediately contacted when a subject is discontinued from blinded investigational product or blinded investigational product is interrupted because of an AE or a laboratory safety test abnormality.

In this trial, a subject may discontinue blinded investigational product 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 investigational product are described in Section 5.8.1.

5.8.1 Follow-up for Subjects Who Discontinue Blinded Investigational Product

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

Subjects who discontinue treatment with blinded investigational product for reasons other than withdrawn consent should attend the clinic for a discontinuation visit followed by a post-treatment telephone call 14 days after the last dose of blinded investigational product. Thereafter, subjects will be followed by telephone contacts according to the study schedule until the end of the trial (Week 104). The purpose of these telephone contacts, as well as the 14-day post-treatment telephone call, is to collect information about subjects' health status (e.g., evaluate if the subject experienced any SAEs or events eligible for adjudication [see Section 7.3.4]).

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 investigational product, and have other study-related procedures conducted at the investigational site) or if the investigator has recommended withdrawal of the subject from active participation in the trial, the investigator must clarify with the subject if he/she is willing to continue in the study with contact at intervals to provide a brief and focused update on health status (e.g., evaluate if the subject experienced any SAEs or events eligible for adjudication [see Section 7.3.4]). **It will be important for the subject to understand the importance of complete collection of information, and also the limited requirements for continuing to provide this information (i.e., a brief telephone contact, occurring at the time of the originally planned study visits).** Thus, subjects may discontinue blinded investigational product and continue to receive telephone calls from the site or they may indicate that they do not wish to have further contact with the site.

Subjects who discontinue treatment with blinded investigational product 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). After discontinuation of blinded investigational product, the Sponsor will continue to reimburse/supply open-label sitagliptin rescue medication (for those rescued) until trial completion (Week 104). 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 two attempts to reach the subject via certified letter. All attempts to contact a subject and information received during contact attempts must be documented in the subject's medical record. If attempts to contact the subject via telephone contacts and certified letters are unsuccessful, alternative measures should be implemented, which may include contacting family members and health care providers and, when applicable, using subject location services. In any circumstance, every effort should be made to document subject outcome, if possible.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

5.11 Clinical Criteria for Early Trial Termination

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

6.0 TRIAL FLOW CHART

Trial Period :	Screening		Run-In	Randomization	Double-Blind Treatment									
					Phase A/Year 1									
Visit Number	1	2[a]	3[a]	4	TC[b]	5	TC[b]	6	7	8	TC[b]	9	TC[b]	10
Scheduled Week			-2	0 (Day 1)	3	6	9	12	18	26	32	39	45	52
Visit Window Guideline (days)			+/-5	+/-5		+/-7		+/-7	+/-7	+/-7		+/-14		+/-14
Administrative Procedures														
Informed Consent[f]	X													
Informed Consent for Future Biomedical Research[g]	X													
Assignment of Screening Number	X													
Contact IVRS	X		X	X		X		X	X	X		X		X
Subject Identification Card		X												
Assignment of Randomization Number				X										
Trial Compliance														
Inclusion/Exclusion Criteria	X		X	X										
Prior/Concomitant Medication Review	X	X	X	X		X		X	X	X		X		X
Diet and Activity Counseling/ Monitoring[h]		X	X	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												
Investigational Product/Rescue Medication														

Trial Period :	Screening		Run-In	Randomization	Double-Blind Treatment									
					Phase A/Year 1									
Visit Number	1	2[a]	3[a]	4	TC[b]	5	TC[b]	6	7	8	TC[b]	9	TC[b]	10
Scheduled Week			-2	0 (Day 1)	3	6	9	12	18	26	32	39	45	52
Dispense Single-Blind Placebo Run-in			X											
Witness Dose of Blinded Investigational Product in Clinic[i]			X	X										
Dispense Double-Blind Investigational Product				X		X		X	X	X		X		X
Dispense Glycemic Rescue Medication as Appropriate						X		X	X	X		X		
Assess Compliance with Blinded Investigational Product				X		X		X	X	X		X		X
Clinical Procedures/Assessments														
Demographics & Medical History	X													
Height	X													
Weight in Duplicate	X	X	X	X		X		X	X	X		X		X
Vital Signs in Triplicate (Pulse Rate and Blood Pressure)	X	X	X	X		X		X	X	X		X		X
Postural (Orthostatic) Blood Pressure/Pulse Rate in Duplicate			X	X		X				X				X
Full Physical Exam			X											
Brief Physical Exam[j]										X				X
12-Lead ECG[k]			X	X										X
Site Fingerstick A1C Measurement[l]	X													
Fasting Fingerstick Glucose in Clinic				X		X		X	X	X		X		X
Review of SMBG Measurements and HAL			X	X	X	X	X	X	X	X	X	X	X	X

Trial Period :	Screening		Run-In	Randomization	Double-Blind Treatment									
					Phase A/Year 1									
Visit Number	1	2[a]	3[a]	4	TC[b]	5	TC[b]	6	7	8	TC[b]	9	TC[b]	10
Scheduled Week			-2	0 (Day 1)	3	6	9	12	18	26	32	39	45	52
Assess Subjects for Potential Rescue or Discontinuation from Blinded Investigational Product, Based on Central Laboratory FPG/A1C						X		X	X	X		X		X
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments														
FPG	X		X	X		X		X	X	X		X		X
A1C[m]	X		X	X		X		X	X	X		X		X
Fasting C-peptide[o]	X[n]			X										X
Proinsulin[o]				X										X
Lipid Panel[p]				X				-		X				X
Chemistry Panel	X			X		X		X	X	X		X		X
Hematology	X			X				X		X				X
Fasting Triglycerides/TSH	X													
Urine Collection (Urinalysis and UrineAlbumin/Creatinine Ratio)[q]		X		X						X				X
Urine Pregnancy Test (women of childbearing potential only)[r]	X		X	X		X		X	X	X		X		X
Plasma and serum for Future Biomedical Research				X										X
Blood (DNA) for Future Biomedical Research				X										

Trial Period :	Double-Blind Treatment				Rescue	Post-Treatment	
	Phase B/Year 2						
Visit Number	11	12	13	14	Rescue[c]	Discontinuation	Follow-up
Scheduled Week	65	78	91	104		At time of Discontinuation[d]	14-Day Post Treatment Telephone Contact[e]
Visit Window Guideline (days)	+/-14	+/-14	+/-14	+/-14			+/-3
Administrative Procedures							
Contact IVRS	X	X	X	X		X	
Trial Compliance							
Prior/Concomitant Medication Review	X	X	X	X	X	X	
Diet and Activity Counseling/ Monitoring[h]	X	X	X	X	X	X	
Investigational Product/Rescue Medication							
Dispense Double-Blind Investigational Product	X	X	X				
Dispense Glycemic Rescue Medication as Appropriate					X		
Assess Compliance with Blinded Investigational Product	X	X	X	X	X	X	
Clinical Procedures/Assessments							
Weight in Duplicate	X	X	X	X	X	X	
Vital Signs in Triplicate (Pulse Rate and Blood Pressure)	X	X	X	X	X	X	
Postural (Orthostatic) Blood Pressure/Pulse Rate in Duplicate					X	X	
Brief Physical Exam[j]				X	X	X	
12-Lead ECG[k]				X		X	
Fasting Fingerstick Glucose in	X	X	X				

Trial Period :	Double-Blind Treatment				Rescue	Post-Treatment	
	Phase B/Year 2						
Visit Number	11	12	13	14	Rescue[c]	Discontinuation	Follow-up
Scheduled Week	65	78	91	104		At time of Discontinuation[d]	14-Day Post Treatment Telephone Contact[e]
Clinic							
Review of SMBG Measurements and HAL	X	X	X	X	X	X	
Assess Subjects for Potential Rescue or Discontinuation from Blinded Investigational Product, Based on Central Laboratory FPG/A1C	X	X	X				
Adverse Event Monitoring	X	X	X	X	X	X	X
Laboratory Procedures/Assessments							
FPG	X	X	X	X	X	X	
A1C[m]	X	X	X	X	X	X	
Fasting C-peptide[o]					X	X	
Proinsulin[o]					X	X	
Lipid Panel[p]				X	X	X	
Chemistry Panel	X	X	X	X	X	X	
Hematology		X		X	X	X	
Urine Collection (Urinalysis and Urine Albumin/Creatinine Ratio)[q]		X		X	X	X	
Urine Pregnancy Test (women of childbearing potential only)[r]	X	X	X	X	X	X	
Plasma and serum for Future Biomedical Research				X	X	X	

Trial Period :	Double-Blind Treatment				Rescue	Post-Treatment	
	Phase B/Year 2						
Visit Number	11	12	13	14	Rescue[c]	Discontinuation	Follow-up
Scheduled Week	65	78	91	104		At time of Discontinuation[d]	14-Day Post Treatment Telephone Contact[e]

a. Subjects on metformin ≥1500 mg/day for ≥8 weeks prior to Visit 1/Screening, with a Visit 1/Screening A1C ≥7.0% and ≤9.0% (≥53 mmol/mol and ≤75 mmol/mol) can directly enter a combined Visit 2/3. Subjects requiring adjustment of blood pressure or lipid-lowering medication and subjects who are not fasting at Visit 1 should NOT have a combined visit. All procedures performed at Visit 2 and Visit 3/Week -2 must be performed at the combined Visit 2/3.
b. Site personnel will contact subjects to assess glycemic control and collect adverse events.
c. Immediately prior to initiation of rescue medication (at a scheduled or unscheduled visit), subjects meeting rescue criteria must undergo the Rescue Visit procedures.
d. Subjects who discontinue taking investigational product prematurely should complete procedures for the Discontinuation Visit. These subjects will also be contacted via telephone by the investigator/qualified designee according to the same schedule as if the subject were still taking investigational product to collect SAEs and events eligible for adjudication (see Section 5.8.1).
e. Subjects will be contacted 14 days after the final dose of blinded investigational product to collect SAEs and events eligible for adjudication.
f. A subject ICF must be signed prior to any trial specific procedures being performed and may be signed prior to Visit 1/Screening.
g. The Future Biomedical Research (FBR) informed consent must be obtained before FBR samples for DNA analysis, plasma, and serum are collected. The FBR sample for DNA analysis should be obtained pre-dose, at Visit 4/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 4/Randomization (pre-dose), Visit 10/Week 52, Visit 14/Week 104 (or Discontinuation Visit), and Rescue Visit (if applicable). 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.
h. Subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at Visit 2 or combined Visit 2/3; follow-up at other visits may be done by other appropriate site personnel evaluating the subject.
i. The witnessed dose will be taken after completion of all procedures for the trial visit, including the collection of all fasting blood samples.
j. Brief physical examination includes assessment of heart, lungs, abdomen, extremities and skin.
k. Visit 3/Week -2 or combined Visit 2/3 ECG is read locally at the investigative site. ECG for all other time points should be submitted to be read centrally.
l. 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.
m. A1C should not be drawn if Discontinuation Visit or the Rescue Visit occurs within six weeks after Visit 4/Randomization (Day 1).
n. Fasting C-peptide test at Visit 1/Screening is only for subjects assessed by the investigator as possibly having Type 1 diabetes.
o. Fasting C-peptide and proinsulin should not be collected for subjects discontinuing in Phase B/Year 2.
p. Includes total cholesterol, high-density lipoprotein (HDL-C) cholesterol, low-density lipoprotein (LDL-C) cholesterol, triglycerides and non-HDL at all time points.
q. Samples should not be obtained if the subject is menstruating, has vigorously exercised within 24 hours or had fever or an active infection within 2 days

Trial Period :	Double-Blind Treatment				Rescue	Post-Treatment	
	Phase B/Year 2						
Visit Number	11	12	13	14	Rescue[c]	Discontinuation	Follow-up
Scheduled Week	65	78	91	104		At time of Discontinuation[d]	14-Day Post Treatment Telephone Contact[e]

of the visit. Under such circumstances, the subject should provide a urine sample at an unscheduled visit.

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.

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 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 after the subject provides written informed consent.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The use of tobacco should be collected as part of the medical history. Additionally, for male subjects, sites must 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 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 Randomization Number

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

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

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

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

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

7.1.1.8.1 Diet and Exercise Counselling and Monitoring

Refer to Section 5.7 for further details.

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

At Visit 2 or combined Visit 2/3, the site will review the symptoms and management of hypoglycemia with the subject. The site will counsel the subject to immediately perform a fingerstick glucose measurement if any symptoms occur that may be related to hypoglycemia (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), but also to avoid delay in treating these symptoms.

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

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

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

Note: As indicated, subjects will record symptoms and/or fingerstick glucose measurements that they believe are related to hypoglycemia on the HAL. Each episode should be evaluated by the investigator. For episodes determined to be hypoglycemia (symptomatic or asymptomatic), and for all glucose values ≤70 mg/dL (3.9 mmol/L) regardless of whether they are considered an adverse event, the Hypoglycemia Assessment (HA) eCRF must also be completed. Each event of symptomatic hypoglycemia must be reported as an adverse event on the adverse 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 7.1.2.13.2.1) 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 or combined Visit 2/3 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 260 mg/dL (14.4 mmol/L) ≥2 times per week. Subjects will be instructed to contact the site if the fingerstick glucose values are ≤70 mg/dL (≤3.9 mmol/L). Furthermore, in order to assess for rescue and/or discontinuation from blinded investigational product, subjects should be instructed to contact the site for fingerstick glucose values that are >270 mg/dL (14.99 mmol/L) after Visit 4/Randomization (Day 1) through Visit 5/Week 6, or >240 mg/dL (13.32 mmol/L) after Visit 5/Week 6 through Visit 6/Week 12, or >200 mg/dL (11.10 mmol/L) after Visit 6/Week 12.

7.1.1.8.4 Witness Dosing

Administration of blinded investigational product will be witnessed by the investigator and/or trial staff at Visit 3/Week -2 or combined Visit 2/3 (start of the placebo run-in) and at Visit 4/Randomization (the first visit of the double-blind treatment period) after completion of all trial procedures including the collection of all fasting blood samples.

7.1.1.8.5 Dispense Single-Blind Placebo Run-in Investigational Product

Subjects will be dispensed single-blind investigational product (ertugliflozin 5 mg and 10 mg matching placebos and glimepiride matching placebo) at Visit 3/Week -2 or combined Visit 2/3 and instructed to take one tablet 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 4/Randomization (Day 1).

Refer to Section 5.2.2 for further details.

7.1.1.8.6 Dispense Double-Blind Investigational Product

Subjects will be dispensed double-blind investigational product (ertugliflozin or matching placebo for ertugliflozin and glimepiride or matching placebo for glimepiride) at all trial visits from Visit 4/Randomization (Day 1) through Visit 13/Week 91 and instructed to take the double-blind investigational product 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 Dispense Open-Label Sitagliptin Rescue Medication (if applicable)

Subjects who meet progressively more stringent glycemic thresholds (see Section 5.6) and have been on the maximum labeled dose (6 or 8 mg q.d.) or on a maximum tolerated dose of glimepiride/matching placebo for at least two weeks will be dispensed open-label sitagliptin at the rescue visit through Visit 9/Week 39.

7.1.1.8.8 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 investigational product.

Compliance with the placebo run-in medication should be monitored by study personnel at the site, at the end of the placebo run-in at Visit 4/Randomization (Day 1), by comparing the returned single-blind investigational product with the amount dispensed and the information reported by the subject. The number of tablets issued minus the number of tablets returned will be used to calculate tablets taken according to the formula below.

Compliance = 100 x (tablets dispensed–tablets returned)/No. of days between visits x No. of tablets taken per day

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 with ertugliflozin/matching placebo and glimepiride/matching placebo will be assessed by subject report. Every effort will be made to maintain adherence as close to 100% as possible.

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Urinary Albumin:Creatinine Ratio (ACR)

A urine sample will be collected on site at the times listed in the Trial Flow Chart – Section 6.0 for measurement of the urinary albumin:creatinine ratio (mg/g). These samples will be used to assess the change in the urinary albumin:creatinine ratio throughout the trial. Samples should not be obtained if the subject is menstruating, has vigorously exercised within 24 hours, or had fever or an active infection within two days of the visit. Under such circumstances, the subject should provide a urine sample at an unscheduled visit.

7.1.2.2 Vital Signs (Sitting Blood Pressure and Pulse Rate)

Vital sign measurements include a triplicate 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 time points 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 triplicate:

- Subjects will 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.
- The appropriate cuff size must be used to ensure accurate measurement. Each subject's cuff size should be noted in his/her source file to assure the same cuff size is used throughout the trial.
- Measurements should be taken on the same arm at each visit (preferably the non-dominant arm).
- Measurements should begin after at least 5 minutes of rest.
- The three measurements of both the blood pressure and pulse rate must be taken approximately 2 minutes apart with the triplicate 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.

7.1.2.3 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 all 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.

7.1.2.4 Body Weight

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

- Weight will be taken ***in duplicate*** throughout the trial at approximately the same time of day, after voiding (i.e., forced void) and while wearing only a gown and underwear (no street clothes, no shoes or socks). Investigator sites without access to gowns should weigh 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 (±0.1 kg) will require corrective action and the sponsor must be contacted. Accuracy checks will be performed approximately monthly and the record of scale accuracy must be sent to the sponsor at the end of the trial.

7.1.2.5 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.

7.1.2.6 Physical Examination

A complete physical examination will be performed at the Visit 3/Week -2 or combined Visit 2/3. A brief physical examination including assessment of the heart, lungs, abdomen, extremities, and skin will be performed at time points noted in the Trial Flow Chart – Section 6.0. Abnormalities considered clinically significant should be reported as adverse events. Other body systems may be evaluated as per the judgment of the investigator or as needed to evaluate adverse events.

7.1.2.7 12-Lead Electrocardiogram

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

- Subjects will refrain from nicotine-containing products and/or ingesting caffeine for at least 30 minutes preceding the procedure.
- 12-lead ECGs should be performed after the subject has rested quietly **for at least 10 minutes** in a supine position.

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

The Visit 3/Week-2 or combined Visit 2/3 ECG should be read and interpreted at the investigative site. ECGs performed at Visit 4/Randomization (Day 1) and time points after randomization should be reviewed at the investigative site for subject safety monitoring, as well as electronically transmitted to a central vendor for reading and interpretation centrally. The investigator is responsible for retaining all copies of the ECG reports.

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

7.1.2.8 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.

7.1.2.9 Fasting Fingerstick Glucose

FFSG values performed in the clinic will be used to assess exclusion criteria prior to randomization at Visit 4/Randomization (Day 1). During the double-blind treatment period, FFSG values performed at home and/or in the clinic will be used to determine the need for titration of glimepiride/matching placebo.

7.1.2.10 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 or combined Visit 2/3 and will be used to determine the need for titration of glimepiride/matching placebo, to assess for events of hypoglycemia, and to determine need for discontinuation from blinded investigational product due to hypoglycemia.

7.1.2.11 Assess Subject for Rescue Based on Central Laboratory FPG or A1C

During Phase A/Year 1, FPG and A1C values obtained at the central laboratory will be used to assess if the subject meets glycemic rescue criteria. Refer to Section 5.6 for further details regarding rescue.

7.1.2.12 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 5.8 for further details regarding discontinuation.

7.1.2.13 Adverse Event Monitoring

7.1.2.13.1 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).

7.1.2.13.2 Hypoglycemia

Based on review of the subject completed HAL at each clinic visit, the investigator must assess the glucose values as well as any symptoms of hypoglycemia reported by the subject. Events of hypoglycemia will be classified by the Sponsor according to the following categories (see Section 8.2.3.2).

Severe Hypoglycemia: An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Fingerstick or plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Documented Symptomatic Hypoglycemia: An event during which typical symptoms of hypoglycemia are accompanied by a measured fingerstick or plasma glucose concentration ≤70 mg/dL (3.9 mmol/L).

Asymptomatic Hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured fingerstick or plasma glucose concentration ≤70 mg/dL (3.9 mmol/L).

Probable Symptomatic Hypoglycemia: An event during which symptoms of hypoglycemia are not accompanied by a fingerstick or plasma glucose determination, but was presumably caused by a plasma glucose concentration ≤70 mg/dL (3.9 mmol/L). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is important to recognize these events as probable hypoglycemia.

Relative Hypoglycemia: An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration >70 mg/dL (3.9 mmol/L). This classification reflects the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels >70 mg/dL (3.9 mmol/L) as plasma glucose concentrations decline toward that level.

7.1.2.13.2.1 Reporting Events of 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 ≤70 mg/dL (3.9 mmol/L) may be reported as an adverse event of "asymptomatic hypoglycemia." General guidance regarding the determination as to whether an event is considered to be an adverse event should be followed (see Section 7.2).

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

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

7.1.2.13.3 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*. 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. 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 will 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.

7.1.2.13.4 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 the central laboratory. The choice and duration of antifungal agent used is left to the investigator or treating physician's discretion.

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 fasting fingerstick glucose measurements, optional site fingerstick A1C at Visit 1/Screening, and all urine pregnancy tests will be performed at the investigational site.

Laboratory test results for chemistry, hematology, urinalysis (except urine glucose), and lipids will not be masked. Glycemic measurements (e.g., FPG, A1C) and C-peptide measurements will be masked from Visit 4/Randomization (Day 1). However, in order for the investigator to perform an evaluation for possible rescue or discontinuation from the blinded investigational product, the central laboratory will report to the investigator in an unmasked manner if an FPG or A1C value meets criteria for glycemic rescue or discontinuation from blinded investigational product criteria (see Sections 5.6 and 5.8).

In addition, the central laboratory will flag the following safety measurements meeting specific criteria for discontinuation from blinded investigational product:

serum creatinine ≥1.5 mg/dL (133 μmol/L) in men or ≥1.4 mg/dL (124 μmol/L) in women;

eGFR <45 mL/min/1.73 m^2;

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;

positive serum pregnancy test

Laboratory safety tests will be performed after at least a 10-hour fast. All laboratory measurements must be performed by the central laboratory.

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, Urinalysis and Others)

Laboratory tests for hematology, chemistry and urinalysis and others are specified in Table 7.

Table 7 Laboratory Evaluations

Hematology	Chemistry	Urinalysis[a]	Others
• Hemoglobin • Hematocrit • RBC Count • Platelet Count • WBC Count • Total Neutrophils (Abs) • Eosinophils (Abs) • Monocytes (Abs) • Basophils (Abs) • Lymphocytes (Abs)	• BUN • Serum Creatinine (eGFR calculated using the MDRD formula) • Calcium (total) • Sodium • Potassium • Chloride • Total Carbon Dioxide (Bicarbonate) • Magnesium • Phosphate • Uric Acid • AST (SGOT) • ALT (SGPT) • Alkaline Phosphatase • Total Bilirubin • Direct (conjugated) Bilirubin[b] • Indirect (unconjugated) Bilirubin[b] • Albumin • Total Protein	• pH • Protein (qual) • Blood (qual) • Ketones • Leukocyte Esterase • Nitrites • Microscopy[c]	• TSH • Fasting C-peptide • A1C • FPG • Proinsulin • Urinary Albumin/Creatinine Ratio[a] • Pregnancy Tests (where applicable) • Lipid Panel (i.e., Total Cholesterol, HDL-C, non-HDL-C LDL-C, and Triglycerides)

[a] Samples should not be obtained if the subject is menstruating, has vigorously exercised within 24 hours, or had fever or an active infection within 2 days of the visit. Under such circumstances, the subject should provide a urine sample at an unscheduled visit.
[b] Both direct and indirect bilirubin measured only when total bilirubin is greater than ULN.
[c] Microscopy performed if the central laboratory dipstick evaluation is positive for blood, nitrites, leukocytes and/or protein. Subjects found to have microscopic hematuria (defined as the presence of three or more red blood cells per high powered field on microscopic examination) from a properly collected, non-contaminated urinalysis with no evidence of infection should be referred to an urologist for appropriate work-up.

Routine laboratory safety tests will be performed after at least a 10-hour fast (i.e., no food, double-blind investigational product, open-label AHA medication [metformin or sitagliptin (if applicable)], or drink except water and non-AHA non-investigational product as prescribed).

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

IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety. The emergency unblinding call center will provide after-hours emergency unblinding coverage when the investigator is not available.

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 Monitor 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.

7.1.5 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 investigational product, open-label AHA medication [metformin or sitagliptin (if applicable)], or drink except water and non-AHA non-investigational product as prescribed) for at least **10 hours** prior to all study visits. Subjects who do not fast before a scheduled visit will be required to return fasting for a study visit within three days. Subjects who have not fasted prior to Visit 1/Screening should obtain a fasting lipid profile and FPG at or prior to Visit 2 rather than Visit 1/Screening. Subjects who have not fasted prior to Visit 1/Screening are not eligible for a combined Visit 2/3.

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 4/Randomization [Day 1] through Visit 8/Week 26) or within +/-14 days (Visit 9/Week 39 through Visit 14/Week 104). 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 Phase A/Year 1 period is as close as possible to 52 weeks. Similarly, the total duration of the combined Phase A/Year 1 and Phase B/Year 2 periods (i.e., the period of time on blinded investigational product) should be as close as possible to 104 weeks. Visits should be scheduled relative to the date of Visit 4/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 investigational product the subject has available.

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

Visit 2 or combined Visit 2/3 may be scheduled as soon as it is confirmed that the subject meets all Visit 1/Screening trial criteria, including laboratory criteria.

The double-blind treatment period begins at Visit 4/Randomization (Day 1). All subsequent double-blind treatment period visits should be scheduled relative to Visit 4/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 to not engage in physically strenuous exercise (i.e., lifting, weight training, calisthenics, and aerobics) within 48 hours prior to their clinic visit.
- The requirement not to take metformin, sitagliptin (if applicable) and blinded investigational product 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 AHAs, the blood glucose meter, the HAL and any collected SMBG information to the clinic.

7.1.5.3 Visit 1/Screening

Subjects will be consented and screened according to Visit 1/Screening Inclusion/Exclusion Criteria and will receive a screening number. 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 and urine 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 3/Week -2 no longer meets the exclusion criterion. Subjects who have lipid-lowering medication adjusted or initiated cannot have a combined Visit 2/3. Subjects on lipid-lowering medication must be on a stable regimen for at least 4 weeks prior to Visit 4/Day 1.

7.1.5.4 Visit 2

At Visit 2, subjects who are (1) on metformin monotherapy ≥1500 mg/day for <8 weeks, (2) on metformin monotherapy <1500 mg/day or (3) on metformin (any dose) in combination with a single allowable AHA will begin the variable wash-off/titration/dose stabilization period. Subjects must be on a stable dose of metformin monotherapy ≥1500 mg/day for ≥8 weeks prior to Visit 3/Week -2. **Subjects on metformin in combination with a SU must complete a ≥10 week dose stable period prior to Visit 3/Week -2.**

All subjects will be evaluated according to Visit 2 Inclusion/Exclusion criteria. The subject's prior/concomitant medications and adverse events will be reviewed, vital signs, body weight, and height will be measured, and fasting urine samples obtained. All subjects will (1) have diet/exercise counseling, (2) receive glucose meters and training in performing SMBG, (3) receive instruction on hypoglycemia symptoms, hypoglycemia management, and completion of the HAL and (4) receive a Subject Identification Card.

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

7.1.5.5 Combined Visit 2/3 or Visit 3/Week -2: Single-blind Placebo Run-in

Subjects with T2DM who are on metformin monotherapy ≥1500 mg/day for ≥8 weeks prior to Visit 1/Screening with a Visit 1/Screening A1C of ≥7.0% and ≤9.0% [53 mmol/mol and 75 mmol/mol] and who meet all other enrollment criteria will be eligible to enter the single-blind placebo run-in at a combined Visit 2/3. All other eligible subjects will undergo a variable wash-off/titration/dose stabilization period prior to Visit 3/Week -2.

The subject's prior/concomitant medications, adverse events, SMBG measurements, and HAL will be reviewed. Vital signs, body weight, and height will be measured, and fasting blood and urine samples obtained. Additionally, a full physical exam, locally read 12-lead ECG and postural blood pressure and pulse will be performed. Women of childbearing potential will have a urine pregnancy test performed (and serum pregnancy test if required by site's IRB/EC).

The first dose of single-blind placebo run-in (matching placebos for ertugliflozin and matching placebo for glimepiride 1 mg) must be taken as a witnessed dose in the clinic visit after completion of all combined Visit 2/3 or Visit 3/Week -2 procedures including the collection of all fasting blood samples. Subjects will take their single-blind placebo for approximately two weeks prior to randomization. Subjects should be reminded to withhold single-blind investigational product on the day of Visit 4/Randomization (Day 1).

7.1.5.6 Treatment Period

7.1.5.6.1 Visit 4/Randomization (Day 1)

At Visit 4/ 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 1:1:1 ratio to ertugliflozin 5 mg q.d., ertugliflozin 15 mg q.d., or glimepiride.

Each subject will be assigned only one randomization number; assignment of a randomization number will occur only at Visit 4/Randomization (Day 1).

Double-blind investigational product will be dispensed at Visit 4/Randomization (Day 1). The first dose of double-blind investigational product should be taken as a witnessed dose after completion of all trial procedures including the collection of all fasting blood samples.

7.1.5.6.2 Visit 5/Week 6 through Visit 14/Week 104: Double-Blind Treatment Period

Subjects will be dispensed double-blind investigational product at Visit 5/Week 6, Visit 6/Week 12, Visit 7/Week 18, Visit 8/Week 26, Visit 9/Week 39, Visit 10/Week 52, Visit 11/Week 65, Visit 12/Week 78 and Visit 13/Week 91.

The blinded investigational product dose must be taken orally in the morning at approximately the same time each day. If a subject misses a dose of blinded investigational product during the trial, they should be instructed to take it as soon as they remember unless it is time for the next dose. Subjects should be instructed not to "make up" for the missed dose by taking two doses at the same time. Compliance for the daily dosed medication will be determined by site performed tablet or capsules count.

7.1.5.7 14-Day Post Treatment Telephone Contact

A telephone contact will be performed 14 days after the last dose of blinded investigational product to collect SAEs and events eligible for adjudication.

7.1.5.8 Follow-up for Subjects Who Discontinue Blinded Investigational Product

Subjects who prematurely discontinue blinded investigational product should be followed according to Section 5.8.1.

7.1.5.9 Follow-up for Subjects Who Discontinue Due to Decreased Renal Function

Subjects who discontinue blinded investigational product for eGFR/creatinine discontinuation criteria (see Section 5.8) or renal-related adverse events should have a repeat eGFR/creatinine performed 1 week after the last dose of blinded investigational product. This post-treatment visit may occur at the Discontinuation Visit (if the Discontinuation Visit occurs 1 week after the last dose of investigational product) or at an unscheduled visit. The out of range test(s) should continue to be repeated at intervals, as considered appropriate (e.g., weekly or every other week) until the value returns to baseline (pre-randomization value) or a new baseline is established. The investigator should implement an appropriate evaluation for events of clinically significant change in eGFR (e.g., >30% reductions in eGFR 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, and microscopic urinalysis (with culture and sensitivity if infection is considered possible), urine creatinine and electrolytes, should be performed, as clinically appropriate.

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 the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

All adverse events will be recorded from the time the consent form is signed through 14 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets.

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

In this trial, an overdose is any dose higher than 100 mg/day of ertugliflozin or matching placebo or any dose higher than 25 mg/day of ertugliflozin or matching placebo for more than 14 days.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

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 or within 14 days of completing the trial. All subjects who become pregnant 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. Sponsor Contact information can be found in the Investigator Trial File Binder.

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

Refer to Table 8 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any subject from the time the consent is signed through 14 days following cessation of treatment, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

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 recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

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.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

All adverse events meeting SAE criteria (see Section 7.2.4) must be reported to the Sponsor within 24 hours of when the site is notified of the event.

The following refers to Sponsor processing of protocol-specified SAEs, but does not impact investigator responsibilities for reporting of any SAE.

Potential pre-specified cardiovascular SAEs will be submitted for adjudication to an independent Clinical Adjudication Committee (CAC) (see Section 7.3.4).

The following potential cardiovascular SAEs will *not be subject* to expedited reporting or unblinding by the Sponsor (ie, if reported as related to blinded investigational product by the investigator), *unless and until* the event is reviewed by the CAC and found not to meet the specified criteria in the CAC charter for that event type:

1. Cardiovascular deaths;

2. Non-fatal myocardial infarction; hospitalization for chest pain or to rule out myocardial infarction, or other hospitalization due to suspected myocardial ischemia where myocardial infarction needs to be ruled out;

3. Non-fatal stroke; TIA, reversible ischemic neurologic deficit (RIND) or other acute ischemic cerebrovascular event where stroke needs to be ruled out;

4. Hospitalization for unstable angina;

As noted above, SAEs that are confirmed by the CAC as one of the pre-specified cardiovascular endpoints (ie, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina) in the meta-analysis of cardiovascular safety *will not be subject to expedited reporting/unblinding by the Sponsor to investigators, Ethics Committees/IRBs and regulatory agencies, regardless of causality*. Note that all SAEs, including confirmed adjudicated cardiovascular events, will be reviewed and monitored by an external data monitoring committee (DMC) unblinded to treatment as part of the overall assessment of safety for ertugliflozin. Based upon their regular review of unblinded safety results, the DMC is empowered by the DMC charter to make recommendations with regard to trial conduct to assure the continuing appropriate safety of the subjects participating in the study.

If an event submitted for adjudication is determined by the CAC *not to meet* the endpoint criteria (for the pre-specified events of CV death, non-fatal MI, non-fatal stroke, or hospitalized unstable angina) in the CAC charter, the event *will then be subject to expedited reporting* (as appropriate, based upon investigator assessment of drug relationship). The SAE awareness date in this instance is identified as the date that the Sponsor or designee receives notification from the CAC that the event does not meet the endpoint criteria.

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 8. The investigator's assessment of causality is required for each adverse event. Refer to Table 8 for instructions in evaluating adverse events.

Table 8 Evaluating Adverse Events

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Executive Oversight Committee

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

7.3.3 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial. The DMC will include 4 clinicians experienced in diabetes and cardiovascular disease and 1 external statistician; this is in addition to the unblinded trial statistician who will be a non-voting member of the committee.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.2.8 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members and the Sponsor and delegate protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor and delegate protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

A DMC recommendation will be communicated to the Sponsor as agreed to in the Collaboration agreement.

7.3.4 Clinical Adjudication Committee

Multiple Clinical Adjudication Committees (CACs) will evaluate the following events:

1. Serious Cardiovascular Events, Venous Thromboembolic Events, and All Deaths: CV disease is a major cause of mortality for subjects with T2DM. In order to evaluate the CV safety of ertugliflozin and meet regulatory requirements for the assessment of CV safety of any new diabetic therapy, serious CV events and all deaths (see below) will be adjudicated in this trial (including events from subjects who continue to be followed after discontinuation of blinded investigational product), and across the Phase II and III ertugliflozin program. The CAC will be comprised of an external panel of independent physicians experienced in assessing cardiovascular endpoints. In addition, venous thromboembolic events and hospitalized heart failure will also be adjudicated to assure a comprehensive assessment of potentially significant cardiovascular events. The panel will be blinded to treatment assignments.

   The events to be adjudicated by the committee include:

   1. All deaths;

   2. Non-fatal myocardial infarction; hospitalization for chest pain or to rule out myocardial infarction, or other hospitalization due to suspected myocardial ischemia where myocardial infarction needs to be ruled out;

   3. Non-fatal stroke (and all events that may be a stroke including all transient ischemic attack (TIA) events, reversible ischemic neurologic deficit (RIND) or other acute ischemic cerebrovascular event where stroke needs to be ruled out)

   4. Hospitalization for unstable angina;

   5. Hospitalization for heart failure;

   6. Venous thromboembolism/pulmonary embolus.

   The criteria to define clinical cardiovascular events will be detailed in the Cardiovascular Adjudication Charter. All potential clinical cardiovascular events will be collected from the first day of double-blind treatment through the end of study (including 14 day post-dose reporting period) for all randomized subjects who have received at least one dose of blinded investigational product. The collection period will continue through study completion/end-of-study whether or not the subject continues to receive blinded investigational product unless the subject is unwilling to be contacted by the personnel at the investigational site.

Clinical cardiovascular events occurring between Visit 1/Screening (the time of informed consent) and Visit 4/Randomization (Day 1) will not be adjudicated.

The identification of a potential clinical cardiovascular event will be made by the trial site or by the Sponsor or designee. The site will communicate the event to the Sponsor or designee within 24 hours of awareness of the potential clinical cardiovascular event using the appropriate CRF module. The Sponsor or designee will in turn provide a listing of specific documents needed to support adjudication by the CAC. Obtaining documentation will be the responsibility of the trial site. Documentation will include, but is not limited to any of the following: hospital discharge summaries, operative reports, clinic notes, ECGs, diagnostic cardiac enzymes, results of other diagnostic tests, autopsy reports and death certificate information. The adjudication charter will contain additional information on source documents to be collected for event adjudication.

The composite of adjudicated events of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina will contribute to a meta-analysis of cardiovascular safety of ertugliflozin across the Phase II and III program.

2. Fractures: In the Phase II study (B152006), following 12 weeks of dosing with ertugliflozin, there was a suggestion of an increase in markers of bone resorption, though there did not appear to be a clear dose-dependent effect with increasing dose of ertugliflozin. In totality, the clinical relevance of these findings remains unclear. However, the effect of ertugliflozin on bone mineral density will be evaluated in a Phase III trial. In addition, in this trial and throughout the Phase III program, all clinical fractures will be adjudicated by an external independent panel of physicians (radiologists) experienced in assessing fractures. The radiologists will review the radiograph(s) (if available) and, where applicable the local radiologist report and other source documents and confirm the presence of the fracture, location of fracture, number of fractures, and type of fracture (i.e., high-trauma, low-trauma, pathological fracture, stress fracture, and other fracture). The panel will be blinded to treatment assignment. A Fracture Adjudication Charter will describe the precise mandates and procedures to be used for the adjudication of clinical fractures.

3. Pancreatitis: Type 2 diabetes is a risk factor for pancreatitis. As part of the overall assessment of the safety profile of ertugliflozin, events of pancreatitis reported in this trial and throughout the Phase III program will be adjudicated by an external panel of independent physicians experienced in assessing pancreatic disease. The panel will be blinded to treatment assignment. A Pancreatitis Adjudication Charter will describe the precise mandates and procedures to be used for the adjudication of pancreatitis.

4. Liver Injury: As hepatic safety is a significant issue in drug development, all events that meet pre-specified criteria for potentially important hepatotoxicity will be adjudicated by an external independent panel of physicians experienced in assessing liver injury. The panel will be blinded to treatment assignment and will assess causality. A Liver Injury Adjudication Charter will describe the precise mandates and procedures to be used for assessing liver injury and assigning causality.

5. Acute Renal Failure: Ertugliflozin, an SGLT2 inhibitor, increases urinary glucose excretion leading to an osmotic diuresis, and has the potential to reduce estimated glomerular filtration rate (eGFR), due to the effect on plasma volume (ie, a hemodynamic effect on eGFR). . As part of the overall assessment of renal safety, events reported in this trial and throughout the Phase III program that meet pre-specified criteria for potentially important renal failure events will be adjudicated by an external independent panel of physicians experienced in adjudication of renal events. The panel will be blinded to treatment assignment and will assess causality. A Renal Failure Adjudication Charter will describe the precise mandates and procedures to be used for assessing renal failure and assigning causality.

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the Adjudication Charter.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Efficacy Analysis

The primary and key secondary endpoints, primary analysis population, and primary analysis method that will be employed for the efficacy analyses are presented in Table 9. To address the primary hypothesis that ertugliflozin is non-inferior to glimepiride in A1C reduction at Week 52, the change from baseline in A1C at Week 52 will be analyzed using a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [15]. The cLDA model will include terms for treatment, time, prior antihyperglycemic medication (monotherapy or dual therapy), baseline eGFR, and the interaction of time by treatment with the restriction of a common baseline mean across treatment groups. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The comparisons of interest will be ertugliflozin 15 mg vs. glimepiride, and ertugliflozin 5 mg vs. glimepiride. The primary hypothesis regarding the non-inferiority of ertugliflozin 15 mg versus glimepiride in decreasing A1C will be assessed using the estimated treatment difference from the cLDA model. If the upper bound of the two-sided 95% confidence interval (CI) for the mean difference between ertugliflozin 15 mg and glimepiride is less than the non-inferiority margin, δ =0.3%, then ertugliflozin 15 mg will be declared non-inferior to glimepiride in terms of A1C reduction at Week 52. The non-inferiority test for ertugliflozin 5 mg in A1C reduction will use the same approach described above for ertugliflozin 15 mg dose level under the multiplicity control strategy described in Section 8.1.3.
Analyses of the change from baseline in body weight and in systolic blood pressure at Week 52 will be performed using the cLDA model as described above.

The primary analysis time point will be Week 52.

Data obtained after the initiation of rescue therapy or after a subject undergoes bariatric surgery will be censored (i.e., treated as missing) in the analyses of efficacy endpoints to avoid the confounding influences of rescue therapy and bariatric surgery. The primary analysis population for all efficacy analyses will be the Full Analysis Set (FAS), comprised of all subjects who receive at least one dose of study therapy and have at least one measurement of the endpoint of interest (either at baseline or post-randomization).

Table 9 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary			
A1C – Change from baseline at Week 52	cLDA	FAS	Model-based
Key Secondary			
Body weight – Change from baseline at Week 52	cLDA	FAS	Model-based
Systolic blood pressure – Change from baseline at Week 52	cLDA	FAS	Model-based

8.1.2 Safety Analysis

The All-Subjects-as-Treated (ASaT) population will be used for safety analyses. Safety and tolerability will be assessed following a tiered-approach by clinical review of all relevant parameters including AEs, pre-defined limits of change (PDLCs; see Section 12.6), laboratory tests, vital signs, and ECG. Adverse events associated with urinary tract infection, male and female genital mycotic infection, hypovolemia and symptomatic hypoglycemia AE will be considered as prespecified safety parameters (Tier-1) for which p-values and 95% confidence intervals (CIs) for between-treatment differences will be provided using the Miettinen and Nurminen method [16]. The AE terms associated with these Tier 1 events will be identified prior to unblinding.

8.1.3 Multiplicity

The type I error rate will be controlled at α=0.05 level (2 sided) for all efficacy hypotheses via a combination of ordered testing and the Hochberg procedure [17] as follows. This strategy is depicted in Figure 2.

- Ordered testing (α=0.05) for the following 6 tests:
    - A1C non-inferiority, ertugliflozin 15 mg vs. glimepiride
    - Hypoglycemia superiority, ertugliflozin 15 mg vs. glimepiride
    - Body weight superiority, ertugliflozin 15 mg vs. glimepiride
    - A1C non-inferiority, ertugliflozin 5 mg vs. glimepiride
    - Hypoglycemia superiority, ertugliflozin 5 mg vs. glimepiride
    - Body weight superiority, ertugliflozin 5 mg vs. glimepiride
- If the success criterion is achieved for all of the above six tests, the Hochberg procedure (α=0.05 or 0.025) will be used for the following two tests:
    - Systolic blood pressure superiority, ertugliflozin 15 mg vs. glimepiride
    - Systolic blood pressure superiority, ertugliflozin 5 mg vs. glimepiride
- If the success criterion is met for both of the above two tests for systolic blood pressure, then the following two tests will be conducted in order (α=0.05):
    - A1C superiority, ertugliflozin 15 mg vs. glimepiride
    - A1C superiority, ertugliflozin 5 mg vs. glimepiride.

8.1.4 Power and Sample Size

The trial will randomize approximately 1230 subjects in a 1:1:1 ratio among the 3 treatment groups. A sample size of 410 per arm will provide 97% power to declare non-inferiority in A1C reduction at Week 52 between a given ertugliflozin dose and glimepiride, using a non-inferiority margin of 0.3%, assuming the true mean difference in A1C is 0%, based on the primary analysis population (FAS). The half-width of the 95% CI is expected to be 0.15%. The probability of meeting the non-inferiority criterion for both ertugliflozin doses in the FAS is 95%. In the secondary analysis population (Per-protocol), the power for declaring non-inferiority is 92% per dose, and 85% for both doses. The above calculations are based on the variability and subject attrition assumptions specified in Section 8.2.6.

8.2 Statistical Analysis Plan

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

The statistical analysis of the data obtained from this trial will be the responsibility of the designee of the Sponsor.

This trial will be conducted as a double-blind trial. After all subjects complete Phase A (Visit 9/Week 52), medical/scientific review has been performed based on Phase A data, protocol deviators based on Phase A have been identified, and Phase A data have been declared final and complete, the trial will be unblinded to the Sponsor or the designee of the Sponsor. A CSR will be generated to support regulatory filing. This report will address the study's primary hypotheses and, hence, is not considered an interim analysis.

After Visit 9/Week 52, investigators and subjects will remain blinded to study drug treatment assignment until all subjects have completed the trial. At the end of the trial (including the 14 days after the last dose of blinded investigational product), the official, final database will be frozen and unblinded after medical/scientific review has been performed, protocol deviators have been identified, and data have been declared final and complete. A separate study report will be prepared after all subjects complete the trial.

8.2.1 Analysis Endpoints

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

The baseline value will be defined as the Visit 4/Week 0/Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after Week -2 will be used as the baseline value. The primary time point of the trial is Week 52.

The mapping of relative day ranges to Week is provided in Section 12.7.

8.2.1.1 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 10. These endpoints will be analyzed at Week 52 as well as at Week 104 where applicable. Week 52 is the primary time point for efficacy analyses. Hypoglycemia is considered a safety endpoint.

In describing the efficacy variables of interest below, the description is restricted to the principal time points of interest (Week 52 and Week 104). However, many variables will be measured at additional time points, as indicated in the Trial Flow Chart (Section 6.0), and may be summarized at other time points.

Table 10 Efficacy Endpoints

Primary Endpoint
Change from Baseline in A1C
Key Secondary Endpoints
Change from Baseline in Body weight Systolic blood pressure
Other Endpoints
Change from Baseline in FPG Proinsulin C-peptide Proinsulin/C-peptide ratio Homeostatic Model Assessment of β-cell function (HOMA-%β) Diastolic blood pressure
Proportion of subjects with an A1C <7.0% and <6.5%
Coefficient of durability (defined in Section 8.2.3.1)
Proportion of subjects with an A1C decrease >0.5% with no symptomatic hypoglycemia and no body weight gain
Proportion of subjects with an A1C < 7.0% with no symptomatic hypoglycemia
Time to rescue
Proportion of subjects requiring rescue medication

8.2.1.2 Safety Endpoints

The descriptions of the safety measurements and time points at which they are measured are provided in Section 4.2.3.2 and Section 6.0 (Trial Flow Chart), respectively. Tier 1 safety endpoints are listed in Table 13.

Part of the assessment of laboratory safety will be accomplished by defining limits of change for particular tests such that occurrences of subject values beyond these bounds are considered abnormal. Limits of change criteria are provided in Section 12.8. These criteria are based upon the laboratory normal ranges and abnormalities considered to be potentially clinically meaningful.

8.2.1.3 Derivation of Efficacy Endpoints

The Homeostasis Model Assessment (HOMA) estimates steady state beta cell function (%β) as a percentage of a normal reference population. This endpoint will be derived using the updated HOMA model [18]. Fasting glucose and C-peptide will be used to calculate beta cell function (%β) using the calculator released from The University of Oxford in 2004 [19].

The Coefficient of Durability is described in Section 8.2.3.1.

Continuous endpoints that are a composite of more than one individual continuous endpoint (such as HOMA %β and the ratio of proinsulin to C-peptide) must be computed based on samples collected on the same day.

8.2.2 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 and treated subjects.

8.2.2.1 Efficacy Analysis Populations

The FAS population will be the primary analysis population for all efficacy endpoints.

For analyses that use the cLDA model described in Section 8.2.3.1, the FAS population, defined separately for each analysis endpoint, consists of all randomized subjects who:

- receive at least one dose of study treatment;
- have a baseline measurement or a post-randomization measurement for the analysis endpoint subsequent to at least one dose of study treatment.

For secondary analyses that use the ANCOVA model with last-observation-carried-forward, the FAS population consists of all randomized subjects who took at least one dose of study treatment, and have measurements for the analysis endpoint both at baseline and at one or more post-baseline time points.

A secondary population for analyzing primary and key secondary efficacy endpoints at Week 52 and Week 104 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 in the day range for the time point of interest (Week 52 or Week 104), without any of the following protocol deviations will be included in this population.

- Drug compliance <75%, using the compliance definition provided in Section 8.2.9.
- Use of prohibited antihyperglycemic medications (found in Section 5.5) for a total of ≥14 days or ≥7 consecutive days after randomization and within 180 days prior to the analysis time point.
- Use of pharmacologic doses of corticosteroids for ≥2 consecutive weeks after randomization and within 180 days prior to the analysis time point
- Incorrect double-blind study medication, or a change in metformin dose, for ≥14 consecutive days during the last 180 days of the trial period of interest

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 patient meeting any of the above criteria during the trial period of interest (Week 0 to Week 52 or Week 0 to Week 104) will be excluded from the per-protocol population for that period.

The final determination on protocol deviations, and thereby the composition of the PP population, will be made prior to the final unblinding of the database at Week 52 and Week 104 and will be documented in separate memos.

A modified FAS (mFAS) population, defined as all subjects in the FAS who do not have any of the protocol deviations defined above, will be an additional secondary population. Subjects who discontinue prematurely without a protocol deviation will be included in the mFAS. Analyses will be performed in this population only if its size differs from that of the PP population by more than 2% of patients in any arm.

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

Data after the initiation of rescue therapy or after a subject undergoes bariatric surgery will be censored (i.e., treated as missing) from analyses of efficacy endpoints.

The time-to-rescue analysis will be performed in the All-Subjects-Treated population.

For all efficacy analyses, subjects will be counted in the treatment group to which they were randomized, regardless of the treatment received during the course of the trial. Details on the approach to handling missing data are provided in Section 8.2.3, Statistical Methods.

8.2.2.2 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this trial. The ASaT population consists of all randomized subjects who took at least one dose of trial treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually took for the analysis of safety data using the ASaT population. This will be the treatment group to which they were randomized, except for any subjects who took incorrect trial treatment for the entire analysis period (Phase A or Phase A + Phase B). Such subjects will be included in the treatment group corresponding to the trial treatment actually received.

For lipid panel, laboratory, ECG and vital sign data, at least one measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Safety analysis will be based on observed data only. No imputation will be performed for missing data except where noted otherwise.

8.2.3 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 8.2.3.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.5, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. All statistical tests will be conducted at the α=0.05 (2-sided) level. The primary objective on A1C is based on non-inferiority testing where the confidence interval rather than the p-value will be used to assess the primary hypothesis.

Analyses will be performed for Phase A alone and for Phase A + Phase B. Between-group comparisons for all efficacy and safety endpoints will be performed for both periods. The following comparisons will be made:

- ertugliflozin 15 mg vs. glimepiride
- ertugliflozin 5 mg vs. glimepiride

The results of adjudicated cardiovascular endpoints will not be presented in the clinical study report for this study. Analyses of these endpoints will be performed in the context of an integrated cardiovascular safety analysis involving the entire Phase II/III program. Details of these analyses will be provided in a separate statistical analysis plan.

8.2.3.1 Statistical Methods for Efficacy Analyses

Phase A (Week 0 to Week 52)

The primary efficacy analyses will compare the efficacy of ertugliflozin relative to glimepiride in change from baseline in A1C at Week 52. The mean change from baseline in A1C at Week 52 in the ertugliflozin 15 mg group will be compared to that in the glimepiride group using the estimated treatment difference via a constrained longitudinal data analysis (cLDA) model, proposed by Liang and Zeger [15]. This cLDA 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 values and the values observed at each post-baseline time point. The cLDA model will include terms for treatment, time, prior antihyperglycemic medication (monotherapy or dual therapy), baseline eGFR, and the interaction of time by treatment. Time will be treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The treatment difference in terms of mean change from baseline to a given time point will be estimated and tested from this model. Ertugliflozin 15 mg will be declared non-inferior to glimepiride in terms of A1C reduction if the upper limit of the two-sided 95% confidence interval (CI) for the mean difference between ertugliflozin 15 mg and glimepiride at Week 52 is less than the non-inferiority margin, δ=0.3%. This margin was chosen because changes from baseline smaller than -0.3% have limited clinical impact, and the 0.3% margin balances lesser clinical impact with a study sample size that is feasible to conduct. The non-inferiority test for ertugliflozin 5 mg in A1C reduction will use the same approach described above following the multiplicity control strategy in Section 8.2.5. If non-inferiority is declared for ertugliflozin 15 mg, then an assessment of superiority will be conducted following the multiplicity control strategy described in Section 8.2.5. For the cLDA model, the Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make proper statistical inference. An unstructured covariance matrix will be used to model the correlation among repeated measurements and hence avoids the potential bias that could result from the use of specific structured covariance models. If the unstructured covariance model fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance such as Toeplitz can be used to model the correlation among repeated measurements. In this case, the empirical option will be used because the sandwich variance estimator is asymptotically unbiased while the model-based variance estimator can substantially overestimate or underestimate the true variance. The cLDA model uses the maximum likelihood principle to estimate the parameters and account for missing data in an implicit fashion. Values of eGFR that are >120 mL/min/1.73 m^2 will be set to 120 mL/min/1.73 m^2.

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different treatment groups. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal analysis of covariance (ANCOVA) model which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and CIs 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. An example of SAS implementation code is given in Section 12.8.

All other continuous efficacy endpoints will be analyzed using the above cLDA method described for A1C.

An analysis of covariance (ANCOVA) model will be used in the PP population as sensitivity analyses for the primary and key secondary efficacy endpoints at Week 52. The ANCOVA model will include treatment, prior antihyperglycemic medication, baseline eGFR, and baseline value. By definition, there will be no missing outcome data in the PP population.

The ANCOVA model as described above will also be used in the FAS population for the primary and key secondary efficacy endpoints. The last-observation–carried–forward (LOCF) method will be used to impute missing data.

If the size of the mFAS population (described in Section 8.2.2.1) differs from the size of the FAS by >2% in any treatment group, primary and key secondary endpoints will be analyzed in the mFAS population using the same cLDA methodology described for the FAS.

All continuous efficacy endpoints will be summarized and plotted over time by treatment group.

For the analysis of percentages of subjects at the A1C goals of <7.0% and <6.5% at Week 52, the constrained longitudinal data analysis (cLDA) model that is used for the analysis of A1C will be used to impute the missing data for 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. The seed for the random number generator will be 8835002. Observed data will not be imputed. Subjects will be categorized as at or not at the A1C goals (<7.0% or <6.5%) at Week 52 after imputation. An additional analysis of the percentages of subjects at A1C goals will treat all subjects with missing Week 52 data as not being at goal, regardless of the final observed A1C value.

To estimate the odds ratio, each of the 10 imputed data sets will be analyzed by logistic regression. The logistic regression model will include terms for treatment and baseline A1C. Parameter estimates on log odds ratio will be combined using standard multiple imputation techniques proposed by Rubin [20] to yield an overall estimate of log odds ratio. Log odds ratio will be back transformed into odds ratio for final reporting.

A time-to-rescue analysis will also be performed. The proportion of subjects rescued in each treatment group will be summarized. Plots of the Kaplan-Meier estimate of the distribution of the time-to-rescue will be provided for each treatment arm and log-rank tests comparing the time-to-rescue distribution of ertugliflozin at a specific dose level versus glimepiride will be conducted. In this analysis, subjects will be censored at the time of discontinuation.

To assess the overall benefit of the trial treatment, the proportion of subjects meeting the composite endpoint of an A1C decrease >0.5% with no AE of symptomatic hypoglycemia and no weight gain by the end of Week 52 will be analyzed using the M&N method in the FAS population for both A1C and body weight at Week 52 [16]. Additionally, the proportion of subjects with an A1C < 7% with no symptomatic hypoglycemia at Week 52 will be analyzed using the same MN method in the FAS population for A1C. For both composite endpoints, missing data will be imputed via the LOCF method.

Durability of the ertugliflozin treatment effect will be evaluated by examining the time profile plot of mean change from baseline in A1C from Week 26 to Week 52, and from Week 26 to Week 104 for each group. In addition, the coefficient of durability (COD), defined as the slope of the time profile of mean change from baseline, will be derived via least squares from the cLDA model, using analysis time points beginning with Week 26. The estimation of COD provides a quantitative assessment for the rate of deterioration of a treatment after reaching its peak efficacy. A treatment with larger COD tends to be less "durable" than a treatment with smaller COD. The COD and its 95% CI will be provided. Standard errors for the COD will be computed by bootstrapping subjects within treatment groups.

A summary of the number (%) of subjects who initiate or have a change in anti-hypertensive medication (new medication or new dose) will be provided. Based on this summary, additional analyses of the blood pressure endpoints that censor data after initiation or changes in anti-hypertensive medication may be performed.

Table 11 summarizes the analysis strategy for all efficacy endpoints. The strategy to address multiplicity issues is described in Section 8.2.5, Multiplicity.

Table 11 Analysis Strategy for Efficacy Endpoints

Endpoint/Variable (at Week 52 unless specified otherwise)	Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Change from baseline in A1C	P S S S	cLDA ANCOVA ANCOVA cLDA	FAS PP FAS mFAS†	Model-based N/A LOCF Model-based
Key Secondary				
Change from baseline in body weight	P S S S	cLDA ANCOVA ANCOVA cLDA	FAS PP FAS mFAS†	Model-based N/A LOCF Model-based
Change from baseline in systolic blood pressure	P S S S	cLDA ANCOVA ANCOVA cLDA	FAS PP FAS mFAS†	Model-based N/A LOCF Model-based
Other Endpoints				
Change from baseline in • FPG • C-peptide • Proinsulin • Proinsulin/C-peptide ratio • HOMA-%β • Diastolic blood pressure	P	cLDA	FAS	Model-based
Proportion of subjects with A1C at goal (<7.0%, <6.5%)	P S	Logistic Regression	FAS	Multiple Imputation Missing=Not at Goal
Coefficient of durability	P	cLDA & bootstrap	FAS	Model-based
• Proportion of subjects with an A1C decrease >0.5% with no symptomatic hypoglycemia and no body weight gain at Week 52 • Proportion of subjects with an A1C < 7% with no symptomatic hypoglycemia	P	M&N	FAS	LOCF
Time to rescue Proportion of subjects requiring rescue medication	P	Kaplan Meier Log-rank	AST	N/A

P=Primary; S=Secondary; M&N=Miettinen and Nurminen
†Analysis will be performed only if the sizes of mFAS and FAS differ by >2% in any treatment arm.

Week 0 to Week 104 Analyses

All endpoints in Table 11 that are collected at Week 104 will also be analyzed at Week 104. Between-group comparisons will be provided for Week 104. Statistical models and analysis populations for Week 104 will be analogous to those at Week 52.

Missing Data

The estimand for the primary efficacy analyses is the treatment effect (ertugliflozin vs. glimepiride) among all randomized subjects at Week 52. It is expected that the primary analysis population (FAS, defined in Section 8.2.3) will include >98% of randomized subjects.

Among subjects in the FAS, some missing outcome data are expected. Identifying the reasons for missing data is an important step in assessing the appropriateness of the models used in the statistical analyses. One source of missingness will be subject discontinuation. Subjects may be discontinued according to protocol specified criteria related to lack of glycemic efficacy. Other discontinuation reasons include laboratory safety measurements outside acceptable limits, AEs, relocation, withdrawal of consent, and violation of the protocol. Another source of missingness will be censoring: efficacy data will be treated as missing following initiation of glycemic rescue therapy.

Missing data mechanisms are often classified as Missing Completely at Random (MCAR), where the missingness does not depend on the observed or the missing data; Missing at Random (MAR), where the missingness is due to only the observed data; and Missing Not at Random (MNAR), where missingness is due to unobserved data. Some of the reasons for discontinuation, such as relocation and lack of efficacy, are likely to be MCAR or MAR, while any mechanism might underlie the other reasons. The mechanism for missingness due to rescue is MAR because the decision to initiate rescue is based on observed data. Of note, the thresholds for initiating rescue are progressively stricter over time, so it is possible for subjects who experience a reduction in glycemic levels to require rescue therapy. If any specific reason for missingness, even if unobserved, is primarily caused by treatment, the mechanism is MAR.

The cLDA method is a full likelihood model that does not require imputation of missing data and produces unbiased inference under MCAR and MAR, which are the mechanisms expected to underlie the majority of missingness in this study.

A detailed accounting of missingness will be provided. To address the robustness of the primary efficacy analyses to the impact of missing data, the following sensitivity analyses will be performed for analyses of A1C.

- Imputation of "Missing=Not at Goal". The percentages of subjects at target A1C control at Week 52 will be analyzed assuming that all missing Week 52 A1C values were not at target.
- LOCF. Endpoints analyzed via cLDA will be re-analyzed using ANCOVA using the last-observation-carried-forward approach to impute missing values.
- Additional models. Specific details for these models will be provided prior to unblinding.
    - Models 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 8.2.10), at least one model will account for compliance.

Further investigation will be performed if the results from these sensitivity analyses are not consistent with results from the primary analyses.

8.2.3.2 Statistical Methods for Safety Analyses

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

Safety analyses will be performed for three time periods: Week 0 to Week 52 (Phase A), Week 52 to Week 104 (Phase B), and Week 0 to Week 104 (Phase A+B). Phase A is considered the primary time period for safety evaluation. All safety endpoints will be analyzed for the Phase A and Phase A+B time periods. For the Phase B time period, only AEs and PDLC in laboratory parameters will be analyzed. The population for analyses of only Phase B will be all subjects who took at least one dose of study medication in Phase B.

Two sets of data will be considered: data pertaining to the Treatment Period and data pertaining to all post-randomization follow-up. For AEs, the Treatment Period dataset will include all data from randomization to 14 days after the final dose of study medication, with the exception of analyses of the Phase A Treatment Period, for which the 14 additional follow-up days will be included only for subjects who did not continue into Phase B. For laboratory endpoints, the Treatment Period dataset will include all data from randomization to 2 days after the final dose of study medication. The "all post-randomization follow-up" dataset, which applies only to SAEs, will include all data after randomization, with no upper limit on the follow-up window. Listings of AEs (regardless of seriousness) and of PDLCs occurring beyond the Treatment Period will be provided. Laboratory data collected after the Treatment Period will be summarized separately from Treatment Period data.

Two approaches will be used for handling data occurring after the initiation of glycemic rescue therapy. The first approach, which will be used for all safety endpoints in analyses of Phase A alone, will exclude all data following the initiation of rescue therapy at any timepoint, in order to avoid the confounding influence of the rescue therapy. The second approach, which will be used for all safety endpoints in analyses of Phase A alone and of Phases A+B combined, will include data following the initiation of rescue therapy. For analyses of Phase A alone, the "including rescue" approach will be considered primary for analyses of SAEs, discontinuations due to AEs, and ECGs, and the "excluding rescue" approach will be considered primary for all other endpoints. For analyses of hypoglycemia, the "excluding rescue" approach will be considered primary regardless of the time period being summarized. For analyses of Phase B alone, excluding/including rescue is not relevant, as there is no rescue therapy in Phase B.

Table 12 summarizes the analysis approaches for safety endpoints by study phase.

Table 12 Safety Analyses by Study Phase

Study Phase(s)	Data Included	Endpoints
A	Treatment Period data, ER	All safety endpoints
	Treatment Period data, IR	All safety endpoints
	All post-randomization data, IR	SAEs, Discontinuations due to AEs
B	Treatment Period data	AEs, PDLCs
A+B	Treatment Period data, IR	All safety endpoints
	Treatment Period data, ER	Hypoglycemia
	All post-randomization data, IR	SAEs, Discontinuations due to AEs
Treatment Period includes up to 14 days post treatment for AEs, and up to 2 days post treatment for PDLCs. ER = excluding data after initiation of glycemic rescue therapy IR = including data after initiation of glycemic rescue therapy		

The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Between-group comparisons will be made between ertugliflozin and glimepiride. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse events (overall summary, specific terms, and system organ class terms) and predefined limits of change in laboratory parameters that are not pre- specified as Tier 1 endpoints 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 or meet PDLC criterion; all other AEs and PDLCs will belong to Tier 3.

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

Continuous measures such as changes from baseline in laboratory, ECG, and vital signs parameters 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 and percent change from baseline over time will be plotted with the corresponding standard errors. Any meaningful differences between these two approaches will be investigated further.

Percent change from baseline for all continuous endpoints in the lipid panel other than triglycerides will be analyzed using the cLDA method as described in Section 8.2.3.1. The cLDA model will include terms for treatment, time, and the interaction of time by treatment. Because the percent change in triglycerides typically has a skewed distribution, the cLDA model which is based on the symmetric normal distribution is not appropriate. Triglycerides will be analyzed using multiple imputation (MI) of missing values (if any) in conjunction with a robust regression (RREG) approach that uses M-estimation. A summary of the number (%) of subjects who initiate or have a change in lipid-lowering medication (new medication or new dose) will be provided. Based on this summary, additional analyses of lipid endpoints that censor data after initiation or changes in lipid-lowering medication may be performed.

Table 13 summarizes the analysis strategy for safety endpoints. Adverse events associated with urinary tract infection, male and female genital mycotic infection, hypovolemia and symptomatic hypoglycemia AEs will be considered as prespecified safety parameters (Tier-1) for which p-values and 95% confidence intervals (CIs) for between-treatment differences will be provided using the Miettinen and Nurminen method [16].

Table 13 Analysis Strategy for Safety Endpoints

Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	AEs associated with urinary tract infection	X	X	X
	AEs associated with genital mycotic infection	X	X	X
	Any AE of symptomatic hypoglycemia	X	X	X
	AEs associated with hypovolemia	X	X	X
Tier 2[1]	Lipid Panel		X	X
	Triglycerides (TG)			
	LDL-C			
	HDL-C			
	Non-HDL-C			
	Total cholesterol			
	AE summary measures		X	X
	Specific AEs[2], SOCs, and PDLC[2]		X	X
	AEs of documented hypoglycemia		X	X
	AEs of severe hypoglycemia		X	X
	Any			
	Requiring medical assistance			
	Not requiring medical assistance			
Tier 3	All endpoints listed under Tier 2 (above) that have incidence <4 subjects in all treatment groups			X
	Additional hypoglycemia adverse event endpoints			X
	Change from baseline results (laboratory measurements, ECG, and vital signs)			X

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

Analysis of Hypoglycemia

The Tier 1 analysis for hypoglycemia, which will be used to address the objectives and hypotheses related to hypoglycemia, will include the numbers and percentages of patients experiencing one or more adverse events of symptomatic hypoglycemia, regardless of biochemical documentation.

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

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

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

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

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

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 patients 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 patients had episodes that were not classified as adverse events, then additional summaries may be provided for the Tier 3 endpoints above, including all episodes reported on the HA eCRF (i.e., not restricted to adverse events). It is expected that all symptomatic hypoglycemia episodes will be classified by the investigator as adverse events and, thus, any episodes that are not classified as adverse events will be asymptomatic episodes.

8.2.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

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

- Continuous baseline demographic variables: age (years), weight (kg), height (cm), and body mass index (BMI; kg/m^2).
- Categorical baseline demographic variables: age (<65 years, ≥65 years), gender (male, female), and race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Multi-Racial), ethnicity (Hispanic/Latino or not).
- Baseline A1C, and distribution of A1C at baseline (A1C levels <7%, ≥7% and <8%, ≥8%)
- Baseline FPG
- Baseline HOMA-%β
- Prior antihyperglycemic medication (monotherapy or dual therapy)
- Time since diagnosis of diabetes mellitus (years)
- Geographic region (Asia, Europe [including Russia] or North America [U.S. and Canada])

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

8.2.5 Multiplicity

The family-wise type I error rate will be controlled at α=0.05 (2-sided) using the testing procedure depicted in Figure 2.

The first six tests will be conducted in a fixed sequence at α=0.05 (2-sided). The non-inferiority hypothesis will be tested using the 95% 2-sided confidence interval (CI) rather than a p-value. If, and only if, all of the first six success criteria are met, the next two tests will be conducted and will use the Hochberg procedure [17]. If, and only if, both tests in the Hochberg procedure are successful, superiority of ertugliflozin to glimepiride will be assessed for the A1C endpoint. This assessment will be performed for each dose of ertugliflozin following a fixed sequence using α=0.05 (2-sided) for each test.

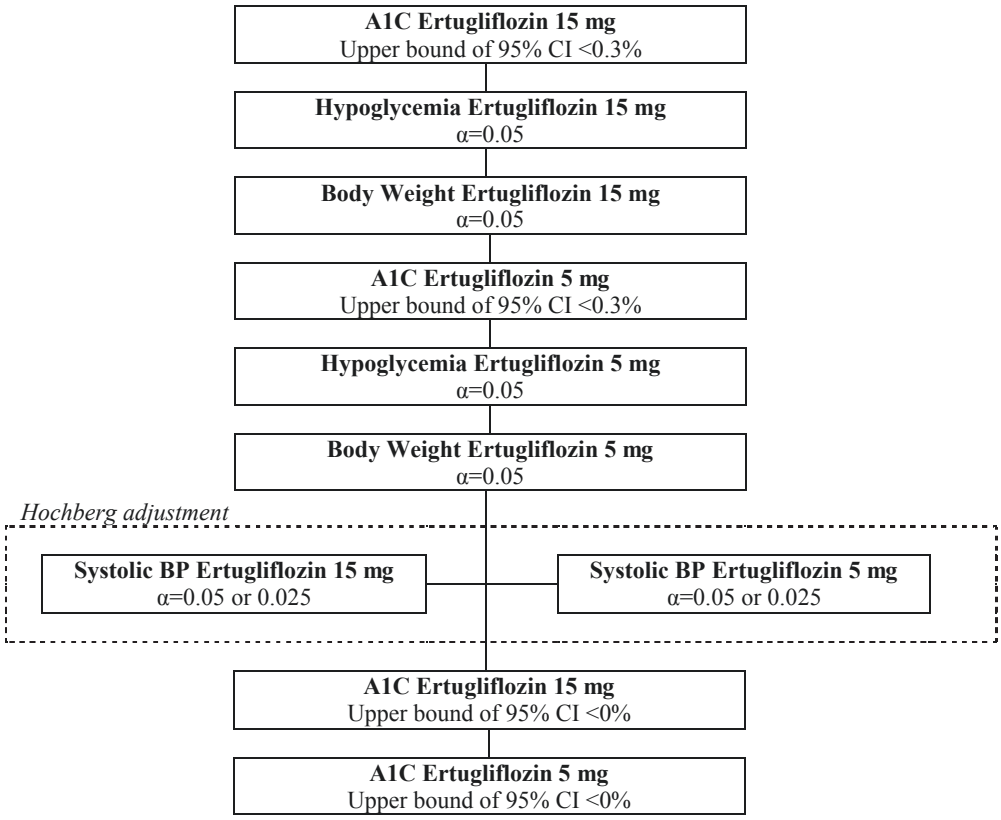


Figure 2 Multiplicity Schema

Comparisons involving other efficacy endpoints and time points are considered supportive and will be made at the α=0.05 nominal level (two-sided). No multiplicity adjustment will be performed on these other comparisons.

From a safety standpoint, application of a multiplicity adjustment could potentially mask a safety concern. Thus, no control of Type I error rate beyond the per-comparison α=0.05 nominal level (i.e. 95% CI) will be applied to the safety analyses, with the realization that spurious statistical significance may be observed for some endpoints.

8.2.6 Sample Size and Power Calculations

This trial will randomize approximately 1230 subjects into three treatment groups in a 1:1:1 ratio. A sample size of 410 per arm will be equivalent to an effective sample size of 337 per arm at Week 52 in the power calculation for the primary hypothesis test using the cLDA model in the FAS population. The effective sample size accounts for information loss due to missing data and the correlation among repeated measures, and is derived using the method proposed by Lu, et al. [21] under the assumptions of cumulative attrition rates and covariance matrix at Weeks 6, 12, 18, 26, 39 and 52 specified below. An effective sample size 337 per arm will provide 97% power to declare non-inferiority for a margin=0.3% in A1C reduction at Week 52 assuming the true mean difference in A1C between a given ertugliflozin dose level and glimepiride is 0% (α=0.05, two-sided test) and the conditional standard deviation is 1.0 % (Table 14).

The half-width of the 95% CI is expected to be 0.15%. The power for achieving success for both ertugliflozin doses will be approximately 95%. In the per-protocol population, the expected sample size is approximately 63% of the randomized population (257 subjects per arm).

Table 14 Power to Declare Non-inferiority in A1C at Week 52

Population	N per Arm	Power		95% CI Half-width
		Per Comparison	Both Comparisons	
FAS	337[†]	97%	95%	0.15%
PP	257	92%	85%	0.17%

[†]Effective sample size, accounting for missing data and within-subject correlation of A1C over time. Based on a non-inferiority margin (δ) = 0.3%, true difference = 0%, standard deviation = 1%, and α = 0.05 (2-sided).

Assumptions for the cumulative attrition rates and correlation matrix at Week 6, 12, 18, 26, 39 and 52 are listed below:

- Cumulative attrition rates at Weeks 6, 12, 18, 26, 39 and 52 are 0.073, 0.091, 0.112, 0.160, 0.210, and 0.312, respectively
- Conditional correlation matrix at Weeks 6, 12, 18, 26, 39 and 52 is

1	0.83	0.71	0.67	0.57	0.57
0.83	1	0.89	0.80	0.68	0.66
0.71	0.89	1	0.90	0.76	0.73
0.67	0.80	0.90	1	0.81	0.77
0.57	0.68	0.76	0.81	1	0.85
0.57	0.66	0.73	0.77	0.85	1

The above assumptions are derived based on data from MK-0431 P024.

Table 15 provides the detectable difference at 90% power for endpoints in the secondary hypotheses in the FAS population.

Table 15 Power Calculations for Key Secondary Endpoints in the FAS Population

Endpoint	Effective Sample Size per Arm	Variability Measurement	Detectable Difference at 90% Power
Proportion of subjects with symptomatic hypoglycemia AEs	410	Proportion for ertugliflozin=5%†	6.2%
Change from baseline in body weight	331	SD=4.3 kg†	1.1 kg
Change from baseline in systolic BP	337	SD=11.2 mm Hg‡	2.8 mm Hg

†Based on canagliflozin study DIA3009.
‡Based on canagliflozin study DIA3012.

8.2.7 Subgroup Analyses and Effect of Baseline Factors

To assess whether the treatment effect at Week 52 is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of the following classification variables:

- Baseline A1C levels: by categories: <8.0%; ≥8.0%
- Age categories: ≤ or > median age
- Gender (female; male)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- BMI (≤ or > median)
- Prior antihyperglycemic therapy (monotherapy or dual therapy)
- Time since diagnosis of Diabetes (≤ or > median years)

For the subgroups that have only 2 categories, if the sample size is not at least 20 subjects in all of the treatment groups in each subgroup category, then that subgroup analysis will not be performed. For the race subgroup analysis, if the sample size is not at least 20 subjects in all of the treatment groups in a certain race category, then that race will be combined with the "Other" race category. The consistency of the treatment effect will be assessed in the context of a repeated measures ANCOVA (RMANCOVA) method, which is a generalization of the standard ANCOVA to accommodate repeated measurements. The RMANCOVA model will adjust for baseline value for A1C, treatment, baseline eGFR, subgroup, and treatment-by-subgroup interaction. Time is treated as a categorical variable and time-specific versions of each term listed above at each week will be used to acknowledge the repeated nature of the measurements. An unstructured covariance matrix will be used to model the correlation among repeated measurements. For subgroup analyses based on factors that are already in the main model, the respective term will appear in the model only once. Treatment effects and nominal 95% confidence intervals by category for the classification variables listed above will be reported as well as presented graphically. Formal statistical testing of treatment-by-subgroup interactions will not be performed.

The treatment effect across trial centers will be summarized for A1C at Week 52 with descriptive statistics.

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

8.2.8 Interim Analyses

In order to support regulatory filings and safety updates, data will be summarized after all subjects complete Phase A (Week 0 to Week 52). Investigators and subjects will remain blinded to study drug treatment assignment until all subjects have completed the trial. This is not considered as an interim analysis.

Confirmed cardiovascular events from this study will be used to perform program-wide meta-analyses to meet regulatory requirements for the assessment of CV safety. The DMC will have the option to recommend an early stop for safety. Aggregate level data on confirmed CV events from this study will be analyzed in a separate report.

8.2.9 Compliance (Medication Adherence)

The computation of compliance will be based on the study medication case report form. Both the assigned treatment and any matching placebo tablets or capsules will be encompassed 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-blinded treatment period will be a compliant day if a patient is compliant for both ertugliflozin/matching placebo and glimepiride/matching placebo (see the definition below); otherwise, it is a non-compliant day. 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 or capsules 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 ertugliflozin/matching placebo or sitagliptin/matching placebo.

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

The definition of compliant days for glimepiride /matching placebo

The compliance will be based on the number of compliant days rather than the number of study therapy tablets or capsules taken because the dosing will vary for different subjects and/or different visits. A day within the double-blind Treatment Period will be considered a compliant day if the subject was compliant on that day with glimepiride or matching placebo, defined as follows:

- the subject took at least one tablet or capsule of glimepiride or matching placebo, or the subject took 0 tablets or capsules of glimepiride or matching placebo with an accompanying indication on the eCRF that this occurred due to the physician's decision to titrate. If only the first in a series of consecutive eCRFs with 0 tablets or capsules recorded has an indication that this occurred due to the physician's decision to titrate, all eCRFs in the series will be considered to represent compliant days.

The definition of compliant days for ertugliflozin /matching placebo

A day within the Double-blind Treatment period will be considered a compliant day to ertugliflozin/matching placebo if the patient reports taking 1 tablet of ertugliflozin 5 mg/matching placebo and 1 tablet of ertugliflozin 10 mg/matching placebo from the correct bottle.

8.2.10 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 16.

Table 16 Product Descriptions

Product Name & Potency	Dosage Form
Ertugliflozin 5 mg	Tablet
Placebo to match Ertugliflozin 5 mg	Tablet
Ertugliflozin 10 mg	Tablet
Placebo to match Ertugliflozin 10 mg	Tablet
Glimepiride 1 mg	Tablet or Capsule
Placebo to match Glimepiride 1 mg	Tablet or Capsule
Glimepiride 2 mg	Tablet or Capsule
Placebo to match Glimepiride 2 mg	Tablet or Capsule

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

All other supplies not indicated in Table 16 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

9.2 Packaging and Labeling Information

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

Subjects will receive blinded bottles, at each visit. No kitting is required.

9.3 Clinical Supplies Disclosure

The central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

9.6 Standard Policies

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

At the close of the trial after unblinding, a letter is to be sent by the investigator to all subjects who received placebo tablets to glimepiride (including those who only received this during the placebo run-in) to inform them that they received look-alike tablets created by the Sponsor to resemble, as much as possible, the drug glimepiride 1 mg and/or glimepiride 2 mg, as manufactured by InvaGen Pharmaceuticals Inc.

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:

A. name, address, telephone number and e-mail address;

B. hospital or clinic address and telephone number;

C. curriculum vitae or other summary of qualifications and credentials; and

D. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed

since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

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 by the Sponsor.

10.7 Publications

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

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

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

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

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

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

11.0 LIST OF REFERENCES

1. American Diabetes Association. Executive summary: Standards of medical care in diabetes - 2012. *Diabetes Care* 2012*;35(*Suppl. 1*):*S4–S10.

2. International Diabetes Federation. Diabetes Atlas. Fifth Edition. Brussels, Belgium. 2011.

3. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013;36:1033-46.

4. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

5. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of Obesity, Diabetes, and Obesity-Related Health Risk Factors, 2001. JAMA 2003:289:76-79.

6. Centers for Disease Control and Prevention. Prevalence of Overweight and Obesity Among Adults with Diagnosed Diabetes - United States, 1988-1994 and 1999-2002. MMWR 2004:53:1066-1068.

7. Stratton IM, Adler AI, Neil HA, et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS35): prospective observational study. BMJ 2000;321:405-12.

8. Isaji M. Sodium-glucose cotransporter inhibitors for diabetes. Current Opinion in Investigational Drugs 2007;8(4):285-92.

9. Abdul-Ghani MA, DeFronzo RA. Inhibition of renal glucose reabsorption: A novel strategy for achieving glucose control in type 2 diabetes mellitus. Endocrine Practice 2008;14:782-90.

10. Bays H. Review: From victim to ally: the kidney as an emerging target for the treatment of diabetes mellitus. Current Medical Research and Opinion 2009;25:671-81.

11. Kim Y, Babu AR. Clinical potential of sodium-glucose cotransporter 2 inhibitors in the management of type 2 diabetes. Diabetes Metab Syndr Obes 2012;5:313-27.

12. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycaemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase III trial. Diabetes Care 2010;33:2217–24.

13. Korytkowski MT. Sulfonylurea treatment of type 2 diabetes mellitus: focus on glimepiride. Pharmacotherapy 2004;24(5):606-620.

14. Davis SN. The role of glimepiride in the effective management of type 2 diabetes. J Diabetes and its Complications 2004;18:367-76.

15. Liang K, Zeger S. Longitudinal data analysis of continuous and discrete responses for pre-post design. Sankhya. The Indian Journal of Statistics 2000; (Series B): 134-148.

16. Miettinen OS, Nurminen M. Comparative analysis of two rates. Stat Med 1985; 4:213-26.

17. Hochberg, Y. (1988). A sharper Bonferroni procedure for multiple tests of significance. Biometrika 75, 800-2.

18. Levy, JC, Mathhews, DR, Hermans, MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 1998: 21: 2191-2192.

19. University of Oxford HOMA calculator released in 2004 (http://www.dtu.ox.ac.uk/homacalculator/)

20. Rubin DB. Multiple Imputation for Nonresponse in Surveys. 1987; Wiley, New York.

21. Lu K, Mehrotra DV, Liu G. Sample size determination for constrained longitudinal data analysis. Statistics in Medicine 2009; 28:679-699.

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

a. Definitions

- Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]
- Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]
- Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]
- DNA: Deoxyribonucleic acid.
- RNA: Ribonucleic acid.

b. Scope of Future Biomedical Research

The DNA, serum, and plasma specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The DNA, serum, and plasma 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.

c. Summary of Procedures for Future Biomedical Research

- Subjects for Enrollment

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

- Informed Consent

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

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

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

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

- 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.

- 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.

d. 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.

e. 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.

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

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

g. 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.

h. 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.

i. 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.

j. 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.

k. 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.

l. 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.

m. Questions

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

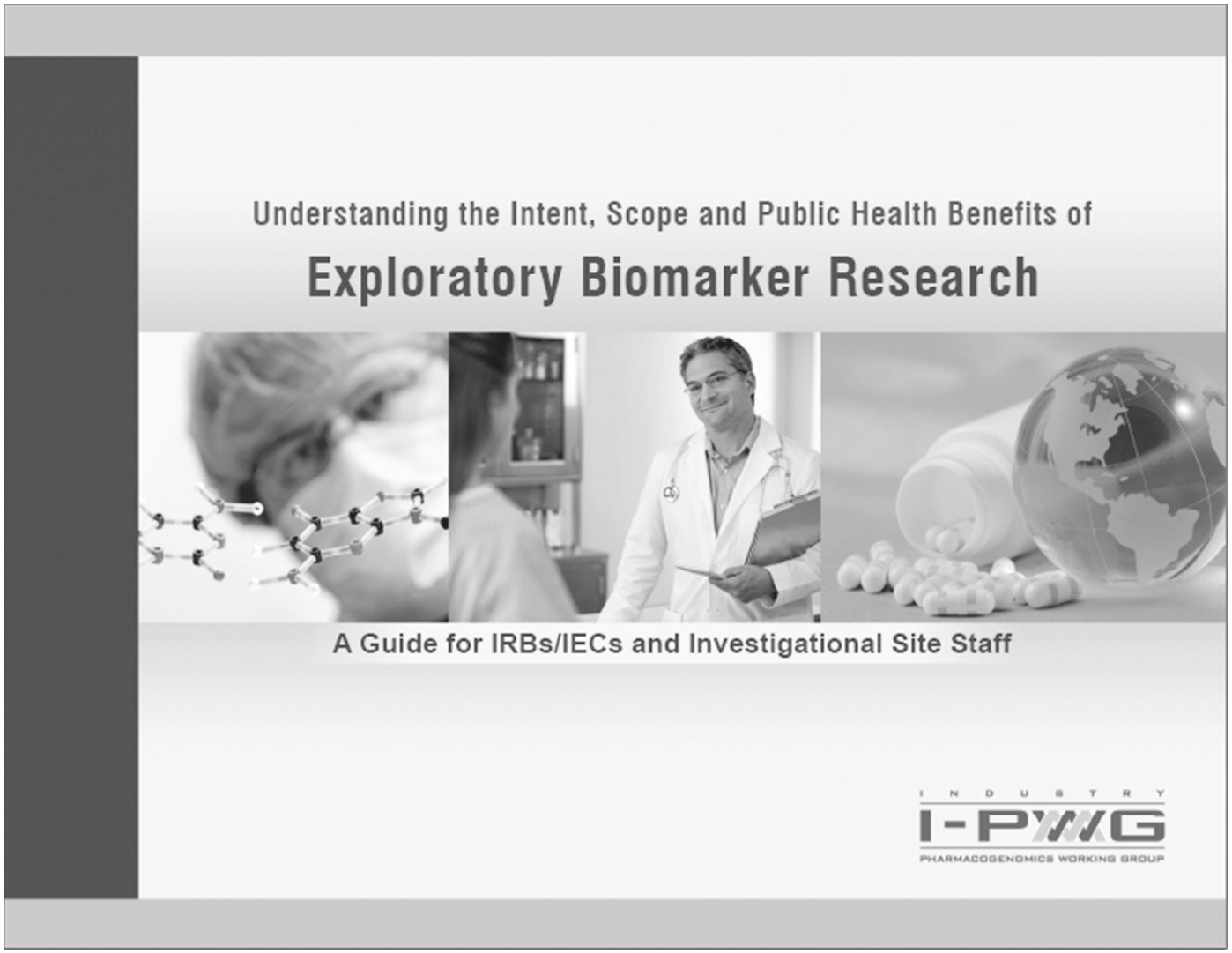
n. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

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

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.

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



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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

1

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

2

I-PWG

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

3

I-PWG

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

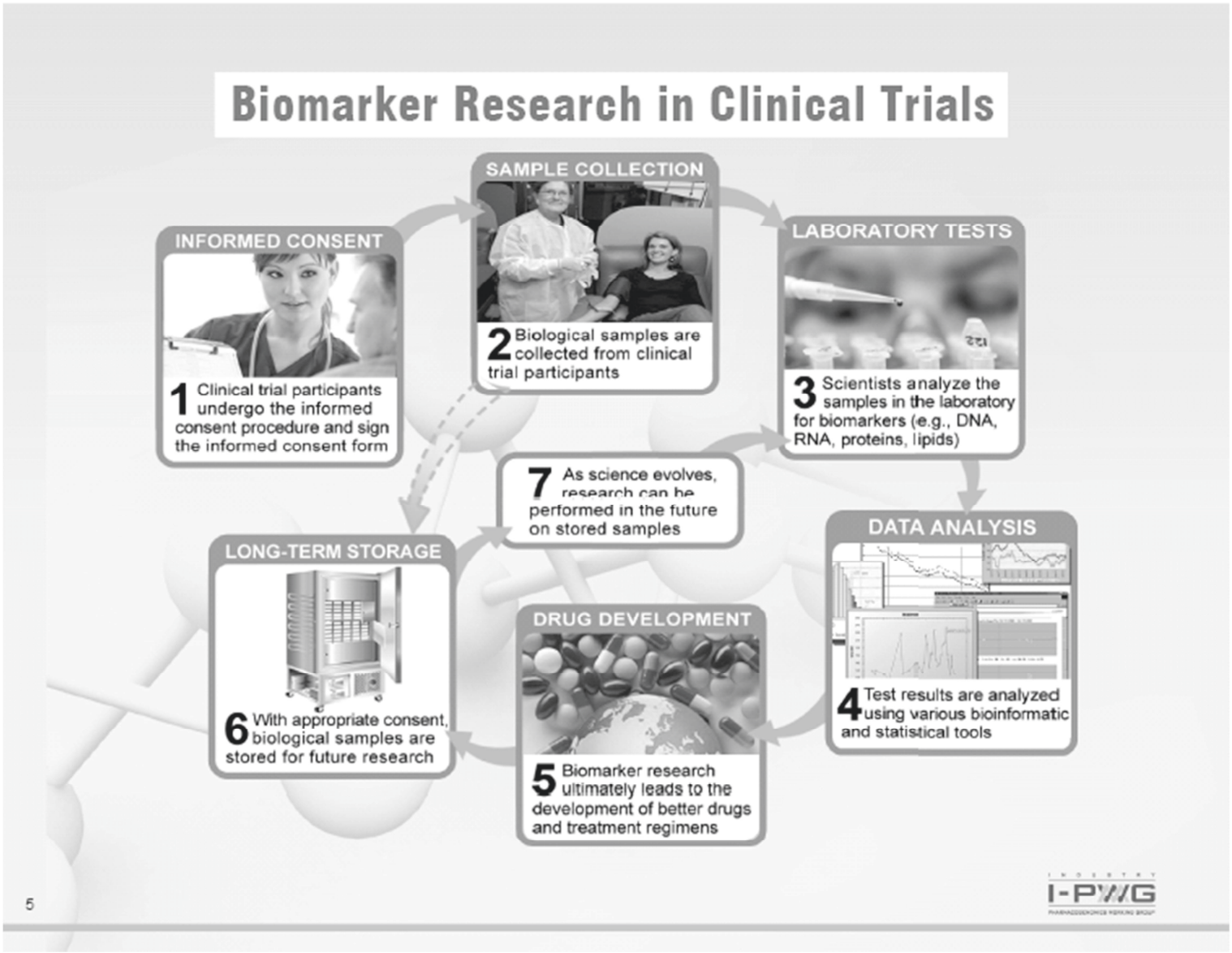
The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible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

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

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

4

I-PWG


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

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.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

6

I-PWG

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

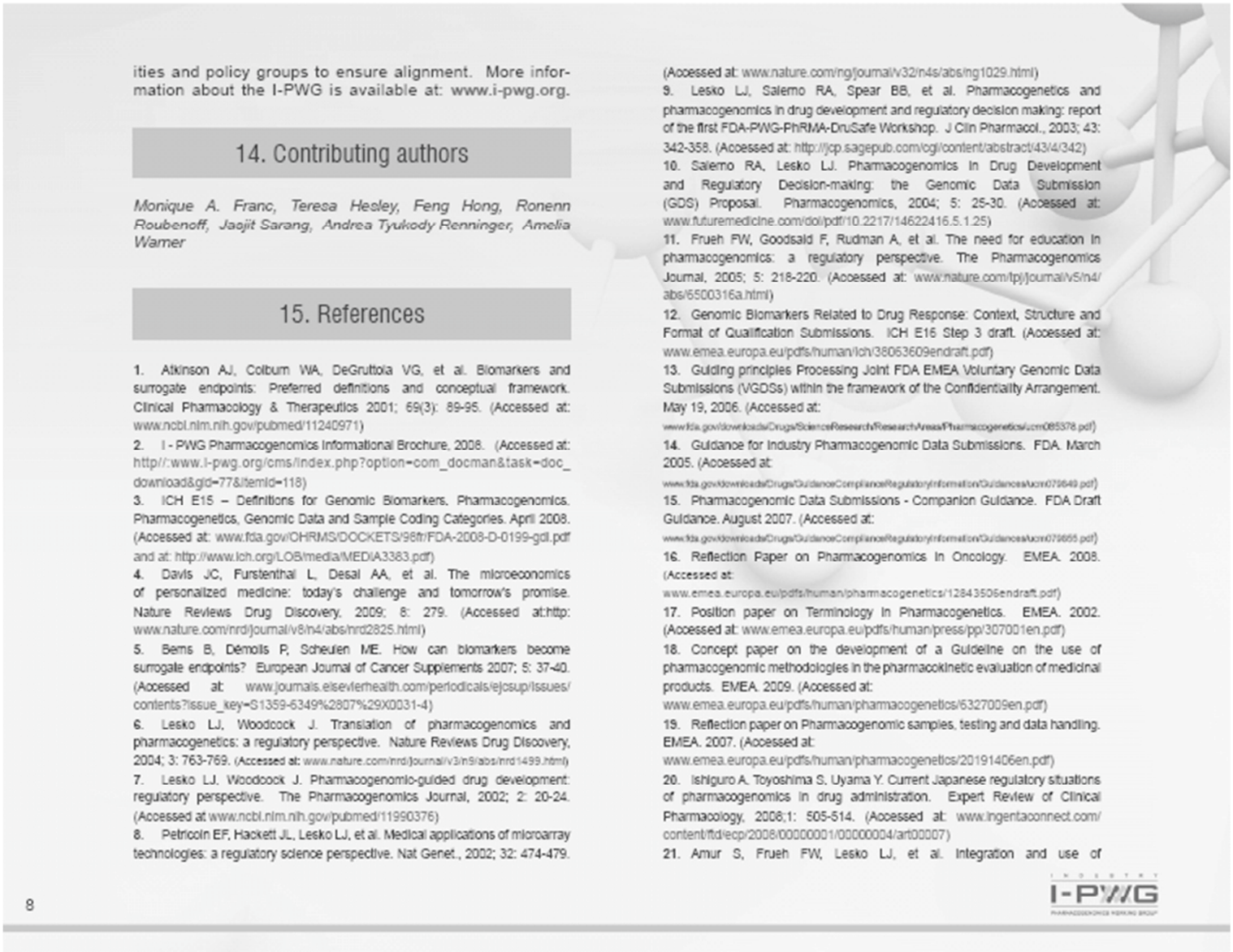
12.Where to Get More Information?

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

13. What is I-PWG?

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

7



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

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jaajit Sarang, Andrea Tyukody Renninger, Amelia Warner

15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)

2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)

3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)

4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)

5. Bems B, Démolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejosup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)

6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)

7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)

8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)

9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)

10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)

11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)

12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/38063609endraft.pdf)

13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)

14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079649.pdf)

15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079665.pdf)

16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)

17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/307001en.pdf)

18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)

19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)

20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/ftd/ecp/2008/00000001/00000004/art00007)

21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

8

I-PWG

biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)

23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)

24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)

25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

26. International Serious Adverse Event Consortium. (Accessed at: www.saeconsortium.org)

27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)

28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)

29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)

30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)

31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MED/A482.pdf)

32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy. 2004; 3: 440-450.

33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)

34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)

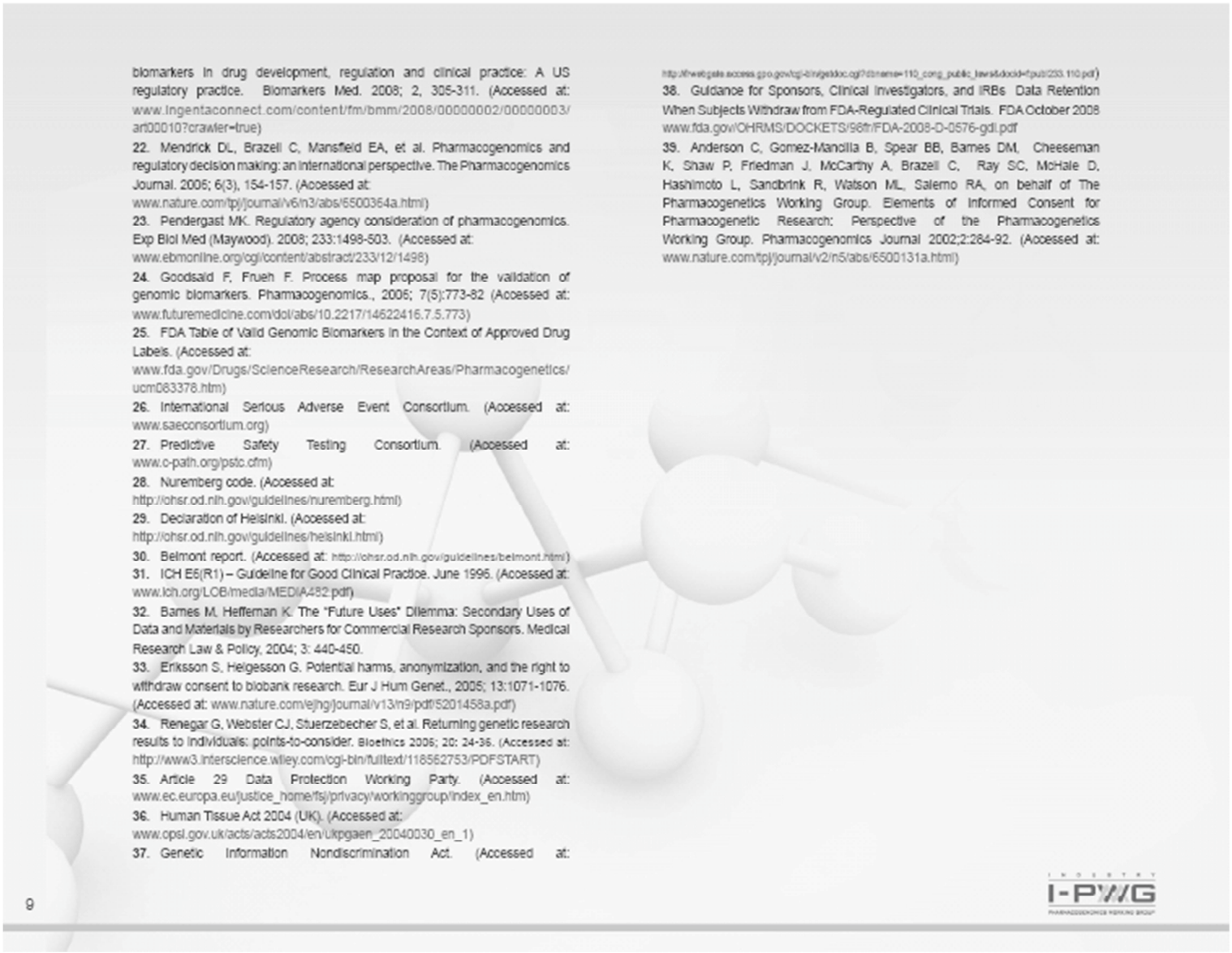
35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)

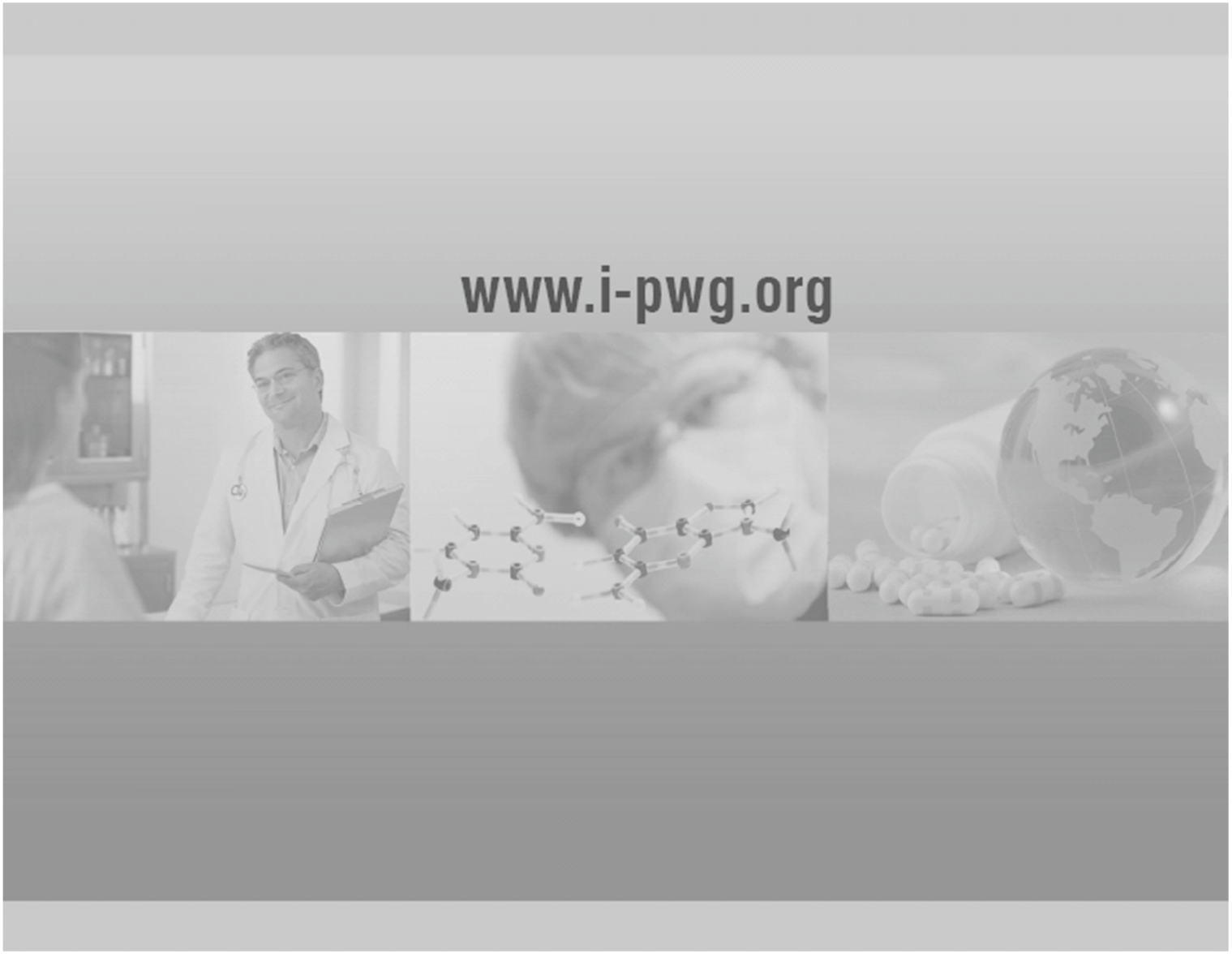
36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)

37. Genetic Information Nondiscrimination Act. (Accessed at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ233.110.pdf)

38. Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf

39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research: Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:284-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)




www.i-pwg.org

12.4 Glimepiride Dosing Instructions

The Glimepiride Dosing Instructions log is an optional tool to help sites instruct subjects how to take glimepiride/matching placebo during the double-blind treatment period (Visit 4/Randomization/Day 1 to Visit 14/Week 104).

Directions:

- Print the *Glimepiride Dosing Instruction* log.
- **Clinic Visits**: The investigator (or designee) should enter the date and dosing instructions for glimepiride/matching placebo (Bottle F [1 mg tablets or capsules] and Bottle G [2 mg tablets or capsules]) and provide the log to the subject.
- **Telephone Contacts**: The subject should enter the date and dosing instructions for glimepiride/matching placebo (Bottles F [1 mg tablets or capsules] and Bottle G [2 mg tablets or capsules]) as specified by site personnel during telephone contacts.

Glimepiride Dosing Instructions

Date (clinic visit or telephone contact)	**Bottle F** (Glimepiride 1 mg or Placebo)	**Bottle G** (Glimepiride 2 mg or Placebo)

12.5 Management of Subjects with Elevated Liver Enzymes (ALT or AST ≥3X ULN)

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

Increases in ALT or AST ≥3X the upper limit of normal (ULN) are defined as clinically significant for this study. The central laboratory report will alert the investigator if a subject meets this threshold. When a randomized subject who is receiving blinded investigational product has an ALT or AST elevation beyond the clinical significant margin above, the investigator should monitor the subject according to the instructions below and discontinue the subject from blinded investigational product if a pre-specified criterion is met.

The investigator should select the appropriate set of instructions (either A, B, or C below) for managing a subject with elevated liver enzymes based upon the following factors: (1) the magnitude of a subject's ALT or AST elevation, (2) the presence or absence of symptoms, (3) whether there is a corresponding increase in total bilirubin (TBL) ≥2X ULN.

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

A) Subject has:

- **ALT or AST ≥3X ULN with TBL ≥2X ULN and alkaline phosphatase (ALP) <2X ULN**

1. The subject should *interrupt* blinded investigational product.
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 investigational product may be restarted with approval by the Sponsor. Otherwise, the subject should discontinue treatment with blinded investigational product.

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 investigational product.

B) Subject has:

- **ALT or AST ≥8X ULN *OR***
- **ALT or AST ≥3X ULN and 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 investigational product.
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 investigational product may be restarted with approval by the Sponsor. Otherwise, the subject should discontinue treatment with blinded investigational product.

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 investigational product.

C) Subject has:

- **ALT or AST ≥3X and <8X ULN**

1. For subjects with:

   ALT or AST ≥3X and <5X ULN:

   - Perform repeat ALT and AST within 3-5 days of receipt of the laboratory report.

   OR

   ALT or AST ≥5X ULN and <8X ULN:

   - Perform repeat ALT and AST within 3 days of receipt of the laboratory report. Subjects unable to undergo repeat measurements within 3 days ***must interrupt*** blinded investigational product.

2. Initiate evaluation for potential causes. See Section II below.

3. Actions based upon ***initial*** repeat testing:

   - If **ALT or AST ≥3X ULN with TBL ≥2X ULN,** then interrupt blinded investigational product and monitor as described in the Section **A** Instructions above and also per 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.

   - If **ALT or AST ≥8X ULN *or* ALT or AST ≥3X ULN with symptoms** present (e.g., fever, eosinophilia, right upper quadrant pain, dark urine, fatigue, etc.), then interrupt blinded investigational product and monitor as described in the Section **B** Instructions above.

   - If **ALT or AST ≥3X ULN and <8X ULN** (without above criteria met), continue to measure ALT and AST 1- to 2-times per week (2-times per week if ALT or AST ≥5X ULN or if an increase >20% occurred since the first elevated value[s]).

   - If **ALT and AST > ULN and <3X ULN**, perform repeat determination in 5-7 days, and then at appropriate intervals (e.g., every other week) until the subject's ALT and AST levels are within normal limits or are similar to baseline.

4. Actions based upon ***follow-up*** repeat testing:

   - If **ALT or AST ≥5X ULN** after 2 weeks, discontinue blinded investigational product.

   - If **ALT or AST remain elevated** (≥3X and <5X ULN) but stable, the frequency of retesting can decrease (e.g., every other week) with approval from the Sponsor.

   - If **ALT and AST >ULN and <3X ULN**, perform repeat determination in 5-7 days, and then at appropriate intervals (e.g., every other week) until the subject's ALT and AST levels are within normal limits or are similar to baseline.

Note: Local laboratory assessments can be used to support compliance with the repeat testing procedures described above if required. Subjects unwilling or unable to undergo repeat ALT and AST testing at the frequency defined above should be discontinued from treatment with blinded investigational product.

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

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

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.

12.6 Predefined Limits of Change (PDLC)

The following predefined limits of change will be assessed in the statistical analysis, as described in Section 8.2.4.2.

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

ECG			
Serum Magnesium	1. Increase ≥1.0 mg/dL and value > ULN 2. Decrease ≥1.0 mg/dL and value < LLN	Y	Y
Serum Phosphate	1. Increase ≥0.5 mg/dL and value > ULN 2. Decrease ≥0.5 mg/dL and value < LLN	Y	Y
QTc (milliseconds)	1. ≥500 msec	N	Y
	1. Increase ≥30 msec and value above gender specific ULN[¶] 2. Increase ≥60 msec and value above gender specific ULN[¶]	N N	Y Y

† Increases and decreases are relative to baseline.
‡ LLN = Lower limit of normal.
§ ULN = Upper limit of normal.
¶ 430 msec and 450 msec for males and females, respectively.

"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 2 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.

12.7 Mapping of Relative Day Ranges to Weeks

The following rules, applicable to all endpoints that (per the study flow chart) are scheduled for collection at all of the time points in the final column below, will be used to map the relative day ranges to weeks, as described in Section 8.2.

Mapping of Relative Day Ranges to Weeks

Required Phase	Relative Day Range	Week
	Visit and/or Day Relative to Start of Trial	
—	Visit <2 and Day <1	min(Day/7[†], -2)
Placebo Run-in	Visit ≥2 and Day <1	-2
Placebo Run-in	Visit ≥3 and Day ≤1	0
A	2 ≤ Day ≤63	6
A	64 ≤ Day ≤ 105	12
A	106 ≤ Day ≤ 154	18
A	155 ≤ Day ≤ 228	26
A	229≤ Day ≤ 319	39
A	320 ≤ Day	52
	Day Relative to the Start of Phase B	
B	1 ≤ Day ≤ 137	65
B	138 ≤ Day ≤ 228	78
B	229 ≤ Day ≤ 319	91
B	320 ≤ Day	104

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

If there are multiple values in the same day range, the last value within that day range will be used for the analysis.

For endpoints that are scheduled to be collected at fewer post-randomization time points, analogous logic to that used above will be applied. For example, Week 26, Week 52, and Week 104 are the only scheduled time points for collection of lipid panel endpoints. The day range for Week 26 will begin at Day 2 and continue until Day 273 (midpoint between 26 weeks and 52 weeks), and the day range for Week 52 will include all Phase A data after Day 273. The day range for Week 104 will include all days within Phase B.

12.8 SAS Code for cLDA Model

Sample SAS code for fitting cLDA model are provided below. This serves as an example only, not the actual implementation codes for this trial. The sample code below assumes that there is a baseline and 4 post-baseline measurements (Weeks 6, 12, 18 and 26) and 2 treatment groups (MK-8835 and placebo).

```
**********************************************************************;

** data step necessary prior to running SAS PROC MIXED;

**********************************************************************;

DATA long; SET long;
ARRAY T{5} t0-t4; * time indicator variables;
ARRAY TT{5} tt0-tt4; * time by treatment indicator variables;
** define week times treatment  indicator variables;
DO i = 1 TO 5;
t{i} = (time=(i-1));
tt{i} = t{i}*(trt=1);
END;
DROP i;
RUN;
**********************************************************************;
** fitting the cLDA model using SAS PROC MIXED;
**********************************************************************;
PROC MIXED DATA=long;
CLASS subj time;  ** subj is the subject id number **;
MODEL y=time tt1 tt2 tt3 tt4;
REPEATED time / SUBJECT=subj TYPE=UN;
ESTIMATE 'T1 Diff (MK-8835-Placebo)' tt1 1;
ESTIMATE 'T2 Diff (MK-8835-Placebo)' tt2 1;
ESTIMATE 'T3 Diff (MK-8835-Placebo)' tt3 1;
ESTIMATE 'T4 Diff (MK-8835-Placebo)' tt4 1;
ESTIMATE 'T1 Placebo LSM' time -1 1 0 0 0;
ESTIMATE 'T2 Placebo LSM' time -1 0 1 0 0;
ESTIMATE 'T3 Placebo LSM' time -1 0 0 1 0;
ESTIMATE 'T4 Placebo LSM' time -1 0 0 0 1;
ESTIMATE 'T1 MK-8835LSM' time -1 1 0 0 0 tt1 1;
ESTIMATE 'T2 MK-8835LSM' time -1 0 1 0 0 tt2 1;
ESTIMATE 'T3 MK-8835LSM' time -1 0 0 1 0 tt3 1;
ESTIMATE 'T4 MK-8835LSM' time -1 0 0 0 1 tt4 1;
ODS OUTPUT Estimates=outm1;
RUN;
```

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

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	SIGNATURE	DATE
_____	_____	_____