Official Protocol Title:	RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO ASSESS CARDIOVASCULAR OUTCOMES FOLLOWING TREATMENT WITH ERTUGLIFLOZIN (MK-8835/PF-04971729) IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS AND ESTABLISHED VASCULAR DISEASE, THE VERTIS CV STUDY
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CLINICAL PROTOCOL

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO ASSESS CARDIOVASCULAR OUTCOMES FOLLOWING TREATMENT WITH ERTUGLIFLOZIN (MK-8835/PF-04971729) IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS AND ESTABLISHED VASCULAR DISEASE, THE VERTIS CV STUDY

VERTIS: eValuation of ERTugliflozin effIcacy and Safety

Compound:	MK-8835/PF-04971729
Compound Name:	Ertugliflozin
United States (US) Investigational New Drug (IND) Number:	106,447
European Clinical Trial Database (EudraCT) Number:	2013-002518-11
Protocol Number:	MK-8835-004-01 (Merck protocol number) B1521021(Pfizer protocol number)
Phase:	3

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

Document History

Document	Version Date	Summary of Changes
Amendment 1	11 March 2016	Added a superiority analysis on the newly-added secondary endpoints of cardiovascular death or hospitalization for heart failure (composite) and cardiovascular death (individual component). Changed the non-inferiority analysis plan: Stage 2 will be only based on the results of the current study and will not be a meta-analysis across Phase 2 and Phase 3. Updated event rate assumption for Major Adverse Cardiovascular Events (MACE) and timing of interim analyses. Changed number of events required at each stage of the analysis and consequently, the amount of alpha to be spent, the power to demonstrate non-inferiority and the time to reach the approximate number of events required at each stage. Updated primary analysis plan for non-inferiority to censor Stage 2 events occurring more than 365 days after last dose of investigational product (IP). Increased the overall sample size to approximately 8000 subjects. Updated assumptions to indicate that the rate of withdrawal from the study will be 5% per year. Order of objectives and endpoints has been changed: all the study specific end points are listed first followed by the primary objective and endpoint for the meta-analysis at Stage 1 for which more details are now provided in the Statistical Analysis Plan. Objectives and Endpoints are now called Primary and Secondary, there is no distinction between cardiovascular and non-cardiovascular. Changed the secondary objective of time to the first occurrence of MACE to time to the first occurrence of MACE plus. Changed the secondary endpoint of: all MACE plus

		events (not censored at time of first event) to: all MACE events (not censored at time of first event). Added secondary end point of: Change in insulin dose from Baseline at Week 18, Week 52 and annually thereafter to the overall study and to the insulin with or without metformin sub-study (at Week 18 only for the sub-study). Added clarification that secondary endpoint of: Time to the first occurrence of a subject receiving glycemic rescue therapy, will only be measured during the first 18 weeks. Added clarification that the analysis of change in albuminuria from baseline is stratified by albuminuria category at baseline. Added a glycemic sub-study in subjects receiving metformin plus sulfonylurea (SU) at the doses specified and clarification regarding inclusion into this sub-study which will be done programmatically at the time of the analyses for all the sub-studies without changing the randomization scheme (only applicable to subjects enrolled prior to amendment). Added inclusion criterion regarding adequate documentation of the objective evidence that the subject has established vascular disease. Previously this wording had only appeared in Section 6.2.1 of the protocol. Modified the exclusion criterion to remove Class III heart failure as exclusionary. Modified laboratory exclusion criteria for screening hemoglobin level as well as clarified repeat screening laboratory test language for certain laboratory parameters. Added language to clarify that the final population for the insulin with or without metformin and for the SU monotherapy sub-studies will be determined via programming at the time of the sub-study analyses. Changed the analysis plan for the SU monotherapy glycemic add-on sub-study to conduct hypothesis

		testing regardless of the number of enrolled subjects in this sub-study. Included new Section on discontinuation of investigational product, withdrawal of consent, and avoiding lost to follow-up (Sections 6.6, 6.7.1 and 6.7.2, respectively) to clarify importance of follow-up of subjects after discontinuation of investigational product and processes to minimize subjects who are lost to follow-up to minimize missing data. Added clarifying wording in Section 7.8 regarding the order of the measurement of postural blood pressure. Added wording in Section 7.9 to clarify the unblinding of fasting plasma glucose (FPG) values of 70 mg/dL or less during the first 18 weeks of the study. Clarified in Section 7.9 that estimated glomerular filtration rate (eGFR) is calculated with the Chemistry analysis. Clarified in Section 7.9, footnote, and in Section 7.9.1 that: If low density lipoprotein (LDL-C) is measured directly on a Day 1 sample, the central laboratory will perform direct LDL-C measurements on subsequent samples for that subject. Corrected in Sections 8.1 and 8.4 the instructions for reporting adverse events (AEs) during the screening period and for the timing of serious adverse events (SAEs) reporting to match Merck´s safety reporting requirements. Added clarification in Section 8.5 that: All adverse events will be reported to regulatory authorities, institutional review boards/ethics committees (IRBs/IECs) and investigators in accordance with applicable local laws and regulations. Updated Section 8.7 to follow Sponsor's instructions for the management of subjects with elevated ALT/AST. Updated Section 1.2.2 to match current Investigator Brochure (IB) document and deleted wording that is a

		repeat from the wording in the IB. Changed the name of the insulin ± metformin sub-study to insulin with or without metformin sub-study to increase clarity about entry requirements. Removed the requirement that for a subject to meet the criterion of either progression or regression of albuminuria, the albuminuria threshold had to be met at two consecutive visits. Clarified in Section 9.7 that only the results of the meta-analysis (Stage 1) will be submitted to regulatory authorities while the main study is ongoing. Added a superiority analysis for the composite endpoint of renal death, renal dialysis/transplant or ≥2x increase in baseline serum creatinine.
Original Protocol	25 August 2013	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), or other bodies.

PROTOCOL SUMMARY

Background and Rationale:

Ertugliflozin (MK-8835/PF-04971729) is a potent inhibitor of Sodium-Glucose co-Transporter 2 (SGLT2) and possesses a high selectivity over glucose transport via Sodium-Glucose co-Transporter 1 (SGLT) and several other glucose transporters (GLUT1-4). Ertugliflozin inhibits renal glucose reabsorption resulting in urinary glucose excretion and thereby reducing plasma glucose and glycated hemoglobin (HbA1c) in subjects with type 2 diabetes mellitus (T2DM). Ertugliflozin is being developed as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

Individuals with T2DM are 2 to 4 times more likely to die from cardiovascular disease than adults without diabetes[1] and coronary heart disease and stroke account for approximately two-thirds of deaths in people with diabetes.[2] Given the substantial cardiovascular morbidity and mortality from T2DM, an understanding of the cardiac safety of a new agent for T2DM is of paramount importance. The United States Food and Drug Administration (FDA) has revised its approval process and guidelines for all new anti-diabetic therapies requiring that acceptable levels of cardiovascular safety are demonstrated at the time of the New Drug Application (NDA) filing as well as post-approval.[3] The European Medicines Agency (EMA) has also updated its guidelines requiring that sponsors of novel diabetes agents demonstrate that the new compound does not increase the risk of macrovascular complications at the time of the Marketing Authorization Application (MAA).[4] Both the FDA and EMA guidance documents recommend that an assessment of cardiovascular safety needs to include subjects with T2DM and elevated cardiovascular risk.

This trial is primarily intended to assess the cardiovascular safety of ertugliflozin and it has two main objectives. First, to support initial regulatory submission, this trial will contribute to a program-wide meta-analysis of cardiovascular endpoints occurring in the ertugliflozin Phase 2 and Phase 3 development program. This meta-analysis is intended to support the initial regulatory submission of ertugliflozin and will assess the composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for unstable angina (MACE plus). This trial will continue in the peri-approval and anticipated post-approval period with the objective of assessing the cardiovascular safety of ertugliflozin on the composite endpoint of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (MACE). The objective of MACE will be based solely on this study and will not use a meta-analysis approach. The primary and secondary objectives for the assessment of the cardiovascular safety of ertugliflozin are listed below.

Additionally, this trial includes a glycemic sub-study in subjects receiving background insulin with or without metformin, another sub-study in subjects receiving background sulfonylurea (SU) monotherapy and a sub-study in subjects receiving background metformin with SU. Details on the objectives and endpoints for these sub-studies are described in the body of the protocol in Sections 2.2, 2.3, 2.4, 2.7, 2.8, 2.9.

Primary Objective and Hypothesis:

- **Primary Objective:** To demonstrate the non-inferiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of MACE: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

- **Hypothesis:** The time to first occurrence of the composite endpoint of MACE in subjects treated with ertugliflozin is non-inferior compared to that in subjects treated with placebo.

Secondary Objectives and Hypotheses

- **Objective**: To demonstrate the superiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of cardiovascular death or hospitalization for heart failure.

- **Hypothesis**: The time to first occurrence of the composite endpoint of cardiovascular death or hospitalization for heart failure in subjects treated with ertugliflozin is superior compared to that in subjects treated with placebo.

- **Objective**: To demonstrate the superiority of ertugliflozin compared with placebo on the time to cardiovascular death.

- **Hypothesis**: The time to cardiovascular death in subjects treated with ertugliflozin is superior compared to that in subjects treated with placebo.

- **Objective**: To demonstrate the superiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of renal death, renal dialysis/transplant, or ≥2x increase in baseline serum creatinine.

- **Hypothesis**: The time to first occurrence of the composite endpoint of renal death, renal dialysis/transplant, or ≥2x increase in baseline serum creatinine in subjects treated with ertugliflozin is superior compared to that in subjects treated with placebo.

- **Objective:** To assess the effect of ertugliflozin as compared with placebo on the time to first occurrence of:

  - MACE plus;

  - Fatal or non-fatal myocardial infarction;

  - Fatal or non-fatal stroke;

  - Hospitalization for heart failure;

  - Individual components of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke).

- **Objective:** To assess the effect of ertugliflozin as compared with placebo on the time to:
  - All-cause mortality;
  - All MACE events (not censored at time of first event);
  - All cardiovascular death or hospitalizations for heart failure (not censored at time of first event.

Objective and Hypothesis Across the Ertugliflozin Phase 2 and Phase 3 Development Program:

- **Objective:** To demonstrate the non-inferiority of ertugliflozin as compared with a non-ertugliflozin comparator group on the time to first occurrence of any of the components of the composite endpoint of MACE plus.
- **Hypothesis:** The time to first occurrence of any of the components of the composite endpoint of MACE plus in subjects treated with ertugliflozin is non-inferior compared to that in subjects not treated with ertugliflozin.

Further details regarding the meta-analysis across the Ertugliflozin Phase 2 and Phase 3 Development Program are provided in the Statistical Analysis Plan (SAP) document.

Endpoints

Primary Endpoint

- The primary cardiovascular endpoint is time to first occurrence of MACE.

Secondary Endpoints

- Time to first occurrence of:
  - Cardiovascular death or hospitalization for heart failure;
  - Cardiovascular death;
  - MACE plus;
  - Fatal or non-fatal myocardial infarction;
  - Fatal or non-fatal stroke;
  - Hospitalization for heart failure;

  - Individual components of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke).

- All-cause mortality.
- All MACE events (ie, not censored at the time of the first event).
- All cardiovascular death or hospitalizations for heart failure (ie, not censored at the time of the first event).
- Time to first occurrence of the composite of renal death, renal dialysis/transplant, or ≥2x increase in baseline serum creatinine.

Endpoint Across the Ertugliflozin Phase 2 and Phase 3 Development Program:

- Time to first occurrence of MACE plus.

Other secondary objectives and endpoints along with primary and secondary objectives, hypotheses and endpoints for the insulin with or without metformin, SU monotherapy and metformin + SU glycemic sub-studies are described in the body of the protocol in Sections 2.1, 2.2, 2.3, 2.4, 2.6, 2.7, 2.8 and 2.9.

Study Population:

Men and women, ≥40 years of age with T2DM (HbA1c 7.0-10.5% [53-91 mmol/mol]) diagnosed in accordance with American Diabetes Association (ADA)[5] guidelines and have established vascular disease involving the coronary, cerebral and/or peripheral vascular systems.

Study Design:

This trial is a multicenter, randomized, double-blind, placebo-controlled, event-driven trial that includes a main cardiovascular study and three 18 week add-on glycemic sub-studies in subjects receiving specific background anti-hyperglycemic treatments. All subjects enrolled under the original protocol prior to Amendment 1 will be randomized into the overall study, and subjects meeting additional inclusion criteria will **also** be included in the specific sub-studies as described below and in Sections 4.1.1, 4.1.2, and 4.2.1. Subjects enrolled after the approval of Amendment 1 will only be randomized into the overall study. For these subjects, the protocol sub-study details described below and in Sections 4.1.1, 4.1.2, and 4.2.1 are not applicable.

Approximately 8000 total subjects will be enrolled and the randomization ratio will be 1:1:1 to 5 mg ertugliflozin once daily, 15 mg ertugliflozin once daily or placebo.

In order to contribute to the program-wide assessment of the cardiovascular safety of ertugliflozin, the cardiovascular endpoints from this trial will be combined with the cardiovascular endpoints from the rest of the Phase 2 and 3 development program to enable a

meta-analysis, provided in the initial registration dossier, to support the cardiovascular safety of ertugliflozin. The endpoint for the meta-analysis will be MACE plus. The goal of this meta-analysis will be to rule out a hazard ratio of 1.8 (an 80% increase in the risk of MACE plus relative to a non-ertugliflozin comparator group).

This trial will continue in the post-approval period to assess the primary endpoint of time to the first occurrence of the composite endpoint of MACE as well as other secondary endpoints. The study's primary hypothesis of non-inferiority of ertugliflozin to placebo will be evaluated by excluding a hazard ratio of 1.3 (a 30% increase in the risk of MACE relative to placebo). If non-inferiority at the 1.3 margin is established for the primary MACE endpoint, then tests of superiority on the secondary endpoints of cardiovascular death or hospitalization for heart failure (composite) and cardiovascular death (individual component) will also be performed. As stated before, this trial is event-driven, with the number of events required to occur prior to assessment of the study's primary endpoint discussed in Sections 3.1 and 9.1.

Beyond the effects on cardiovascular endpoints, the trial is also designed to assess the safety and tolerability of ertugliflozin and its effects on measures of glycemic control, blood pressure, body weight, renal function and albuminuria.

For subjects enrolled under the original protocol, at the time of randomization, subjects will be stratified into the main cardiovascular study, the insulin (with or with metformin) sub-study or the SU monotherapy sub-study, according to their background anti-hyperglycemic treatment as follows. Subjects receiving background insulin (with or without metformin) at doses specified in the protocol are included into the insulin (with or without metformin) add-on glycemic sub study; subjects receiving background SU monotherapy (at doses specified in the protocol) are included into the SU monotherapy add-on glycemic sub-study. Subjects receiving background metformin with SU at doses specified in the protocol are included in the metformin plus SU sub-study. Unlike the other two sub-studies, inclusion in the metformin with SU sub-study will not be determined at the time of randomization. Instead, all subjects randomized into the main cardiovascular study who meet the additional eligibility requirements will be considered enrolled in this sub-study. Since all the subjects participating in the three sub-studies are enrolled in the main cardiovascular study, visit schedules and protocol-required tests and procedures are the same for all subjects irrespective of whether or not a subject also participates in a sub study. The glycemic sub-studies will run during the initial 18 weeks of the study. Following the collection of efficacy and safety end points at Week 18 (V5), subjects in the glycemic sub-studies will continue participating in the main cardiovascular study.

Study Treatments:

Subjects will be randomized in a 1:1:1 ratio to receive ertugliflozin 5 mg, ertugliflozin, 15 mg ertugliflozin or matching placebo once daily added to their background therapy.

Statistical Methods:

Sample Size

The cardiovascular safety of ertugliflozin will be assessed in two stages. Stage 1 will consist of a meta-analysis of MACE plus events across the Phase 2 and Phase 3 development program with the majority of events expected to come from this trial. Stage 2 will consist of an analysis of MACE and secondary endpoints [eg, Cardiovascular (CV) death or hospitalization for heart failure (composite), CV death (individual component), and renal composite] in this trial. The two doses of ertugliflozin (5 and 15 mg) will be pooled for the purpose of all these analyses.

The primary objective for the Stage 1 across-program meta-analysis will be addressed by testing the hypotheses H0: Hazard Ratio (HR)≥1.8 versus H1:HR<1.8 for the MACE plus endpoint; the primary Stage 2 analysis (assessed within this study) will be addressed by testing the hypotheses H0:HR≥1.3 versus H1:HR<1.3 for the MACE endpoint. For these analyses, the HR represents the risk of ertugliflozin relative to a non-ertugliflozin comparator group at Stage 1 and relative to placebo at Stage 2 as measured by the hazard ratio.

Stage 1 of the trial uses a group sequential design with up to two analyses: an interim analysis and a final analysis. The Stage 1 interim analysis will take place at the later of 1) the time at which at least 130 adjudicated MACE plus events have accrued throughout the Phase 2 and Phase 3 development program or 2) the approximate time at which all necessary data are available to support the filing of ertugliflozin. This analysis will assess the hazard ratio for the MACE plus endpoint with respect to the 1.8 non inferiority margin. If the first analysis is conducted with less than 173 MACE plus events, then a second analysis (the final analysis for Stage 1) will take place, if necessary (ie, if the non-inferiority margin of 1.8 is not met in the first analysis), at the time at which at least 173 MACE plus events have accrued, and the appropriate alpha spending will be determined from an O'Brien-Fleming type spending function. If the first analysis is conducted with 173 or more MACE plus events, then that will constitute the only analysis for Stage 1, and the full alpha of 0.025 (1-sided) will be utilized.

For these Stage 1 analyses, using an O'Brien-Fleming type alpha spending function, and analyses at 130 and 173 adjudicated MACE plus events, the meta-analysis will have approximately 95% power to demonstrate non-inferiority of ertugliflozin to a non-ertugliflozin comparator group when there is truly no difference between treatments (HR=1.0) using the non-inferiority margin of 1.8 and testing at the overall one-sided alpha level of 0.025.

Stage 2 of the trial uses a group sequential design with up to two analyses: an interim analysis and a final analysis. The Stage 2 interim analysis and the final analysis are planned to occur when approximately 714 and 939 adjudicated MACE events have accrued in this study. These analyses will assess the hazard ratio for the MACE endpoint with respect to the 1.3 non-inferiority margin. If non-inferiority is established for the primary MACE endpoint, then tests of superiority on the secondary endpoints of CV death or hospitalization for heart

failure (composite), CV death (individual component), and the renal composite will also be performed in a sequential manner. If any of the first three tests in this four step testing sequence are unsuccessful at the interim analysis, the study may be continued to the final analysis (depending on the result of futility assessment).

For the primary Stage 2 analyses, using an O'Brien-Fleming type alpha spending function and analyses at approximately 714 and 939 adjudicated MACE events, the study will have approximately 96% power to demonstrate non-inferiority of ertugliflozin to placebo when there is truly no difference between treatments (HR=1.0) using the non-inferiority margin of 1.3 and testing at the overall one-sided alpha level of 0.025.

With two enrollment periods of 19 months each and assuming an event rate of 3.5% per annum for MACE, a total of approximately 8000 subjects (about 4000 per enrollment cohort) randomized in a 1:1:1 ratio to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo will be sufficient to accrue approximately 714 MACE events within approximately 5.0 years and approximately 939 MACE events within approximately 6.1 years from the start of this study. These calculations assume that subjects will withdraw from the study at a rate of 5% per annum.

Power for Secondary Hypotheses

For the Stage 2 analyses of secondary endpoints, using an O'Brien-Fleming alpha spending approach and assuming accrual of at least 442 and 582 composite events of cardiovascular death or hospitalization for heart failure at the interim and final analysis respectively, the study will have approximately 90% power to demonstrate superiority of ertugliflozin to placebo on the composite endpoint of cardiovascular death or hospitalization for heart failure when the true HR=0.75. Moreover, assuming accrual of at least 287 and 377 cardiovascular death events at the interim and final analysis respectively, the study will have approximately 83% power to demonstrate superiority of ertugliflozin to placebo on cardiovascular death when the true HR=0.725. With accrual of at least 144 and 190 renal composite events at the interim and final analysis respectively, the study will have approximately 79% power to demonstrate superiority of ertugliflozin to placebo on the renal composite endpoint when the true HR=0.65.

Cardiovascular Endpoints Analysis:

The two doses of ertugliflozin will be pooled for the analysis of all cardiovascular endpoints. The analyses described below will be performed at each interim analysis and at the end of the trial.

The Stage 1 meta-analysis population will include all randomized subjects who have taken at least one dose of investigational product across the Phase 2 and 3 development program. The Stage 2 non-inferiority analysis population will include all randomized subjects who have taken at least one dose of investigational product in this study. For both stages, subjects will be analyzed in the group to which they were assigned by the Interactive Voice Response System (IVRS), regardless of the actual treatment received, and only events confirmed by the Endpoint Adjudication Committee will be included in the analysis. For Stage 1, all

confirmed MACE plus events will be included in the primary analysis. For Stage 2, confirmed MACE events occurring between randomization and 365 days after the last dose of study treatment will be included in the primary non-inferiority analysis.

The MACE plus and MACE endpoints will be analyzed using a stratified Cox proportional hazards model including treatment group as a covariate. For the Stage 1 meta-analyses, the Cox model will include "Study" as a stratification factor with the following three levels: cardiovascular study, placebo-controlled non-cardiovascular studies, and active-controlled non-cardiovascular studies. For the Stage 2 analyses, the Cox model will include "Cohort" as the stratification factor with the following levels: Cohort 1 (subjects randomized between December 2013 and July 2015) and Cohort 2 (subjects randomized in 2016 and beyond). A test of non-inferiority at the one-sided 0.025 significance level will be performed based on the Cox model. The upper bound of the alpha-adjusted two-sided confidence interval (CI) for the hazard ratio (HR) (ertugliflozin to a non ertugliflozin comparator group or placebo) will be calculated using an O'Brien-Fleming alpha spending function and compared with the appropriate non-inferiority margin (1.8 or 1.3).

If non-inferiority at the 1.3 margin is established for the primary MACE endpoint based solely on this study, then tests of superiority on the secondary endpoints of cardiovascular death or hospitalization for heart failure (composite), cardiovascular death (individual component), and the renal composite will also be performed. The population for superiority testing will include all randomized subjects and all confirmed events, including those occurring more than 365 days following discontinuation of investigational product. Superiority tests will be implemented by comparing the upper bound of the alpha-adjusted two-sided CI to 1.0.

In order to control the Type I error rate across multiple hypotheses in Stage 2, a four-step hierarchical testing sequence for the pooled ertugliflozin group versus the placebo group will be utilized as follows:

1. Non-inferiority for MACE;
2. Superiority for cardiovascular death or hospitalization for heart failure (composite);
3. Superiority for cardiovascular death (individual component);
4. Superiority for renal death, renal dialysis/transplant, or ≥2x increase in baseline serum creatinine.

Kaplan-Meier curves for the distribution of time to the primary and secondary endpoints will also be provided for each of the three treatment groups.

Subjects without events will be censored at the earliest of the study cut-off date, last contact date, or end of the applicable analysis ascertainment window (eg, 365 days after the last dose of investigational product for primary Stage 2 non-inferiority analyses).

Protocol summary information, when provided, is consistent with and does not contain new information that is not found in the body of the protocol.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Protocol Activities	**Visits During Year 1**								**Visits Following Year 1**		
	V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Weeks (Wk) or Months (M) Since Randomization[a]	**Screening**	**Day 1[b]**	**Wk 6**	**Wk 12**	**Wk 18**	**Wk 26**	**Wk 39**	**Wk 52**	**M 16**	**M20**	**M24**
Recommended Visit Window			**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±14 days**	**±14 days**	**±1 month**	**±1 month**	**±1 month**
Informed Consent	X										
Informed Consent for Future Biomedical Research	X										
Contact IVRS System	X	X	X	X	X	X	X	X	X	X	X
Assess Eligibility	X	X									
Randomization		X									
Provide Subject with Study Contact Card		X									
Demography, Height in Duplicate & Medical History including Smoking	X										
Complete Physical Examination		X									
Brief Physical Examination[c]								X			X
Body Weight	X	X	X	X	X	X	X	X	X	X	X
Sitting Blood Pressure and Pulse Rate[d]	X	X	X	X	X	X	X	X	X	X	X
Postural (Orthostatic)Blood Pressure and Pulse Rate[e]		X	X			X					
12-Lead ECG[f]	X				X			X			X

Protocol Activities	Visits During Year 1								Visits Following Year 1		
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Weeks (Wk) or Months (M) Since Randomization[a]	Screening	Day 1[b]	Wk 6	Wk 12	Wk 18	Wk 26	Wk 39	Wk 52	M 16	M20	M24
Recommended Visit Window			±7 days	±7 days	±7 days	±7 days	±14 days	±14 days	±1 month	±1 month	±1 month
Laboratory											
Chemistry Group	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X		X	X		X			X
Urinalysis[g]	X	X			X	X		X			X
Pregnancy Test (women of childbearing potential only)[h]	X	X	X	X	X	X	X	X	X	X	X
Site Fingerstick HbA1c[i]	X										
Fasting Fingerstick Glucose		X									
Fasting Triglycerides/TSH	X										
HbA1c & FPG	X	X	X	X	X	X	X	X	X	X	X
Lipid Panel[j]		X			X			X			X
Urinary Albumin/Creatinine ratio[k]		X			X			X			X
Whole blood (DNA) for Future Biomedical Research[l]		X									
Plasma for Future Biomedical Research[l]		X			X			X			
Serum for Future Biomedical Research[l]		X			X			X			
Drug											
Dispense Investigational Product		X	X	X	X	X	X	X	X	X	X
Assess Compliance with Investigational Product			X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications Assessment	X	X	X	X	X	X	X	X	X	X	X
Subject Education/Monitoring											
Diet/Exercise Counseling (V2)/Monitoring (other visits)		X	X	X	X	X	X	X	X	X	X
Distribute Sponsor-provided Glucose meter (V2) and Glucose meter Supplies		X	X	X	X	X	X	X	X	X	X

Protocol Activities	Visits During Year 1								Visits Following Year 1		
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11
Weeks (Wk) or Months (M) Since Randomization[a]	**Screening**	**Day 1[b]**	**Wk 6**	**Wk 12**	**Wk 18**	**Wk 26**	**Wk 39**	**Wk 52**	**M 16**	**M20**	**M24**
Recommended Visit Window			**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±14 days**	**±14 days**	**±1 month**	**±1 month**	**±1 month**
Dispense Hypoglycemia Assessment Log and Blood Glucose-Self Monitoring logs and educate on hypoglycemia symptoms and management and on symptoms of hyperglycemia		X									
Dispense/Review self monitoring blood glucose and Hypoglycemia Assessment Log			X	X	X	X	X	X	X	X	X
Adverse Event Monitoring[m]		X	X	X	X	X	X	X	X	X	X
Potential Cardiovascular Event Assessment[n]		X	X	X	X	X	X	X	X	X	X

Protocol Activities	Visits Following Year 1											
	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	
Months (M) Since Randomization[a]	M28	M32	M36	M40	M44	M48	M52	M56	M60[o]	ET[p]/ EOS[q]	2 Week Phone Follow Up[s]	Glycemic Rescue Visit[t]
Recommended Visit Windows	±1 month	±1 month	±1 month	±1 month	±1 month	±1 month	±1 month	±1 month	±1 month		±3 days	
Contact IVRS System	X	X	X	X	X	X	X	X	X	X		
Brief Physical Examination[c]			X			X			X	X		X
Body Weight	X	X	X	X	X	X	X	X	X	X		X
Sitting Blood Pressure and Pulse Rate[d]	X	X	X	X	X	X	X	X	X	X		X
Postural (Orthostatic) Blood Pressure and Pulse Rate[e]												X
12-Lead ECG[f]			X			X			X	X		
Laboratory												
Chemistry Group	X	X	X	X	X	X	X	X	X	X		X
Hematology			X			X			X	X		X
Urinalysis[g]			X			X			X	X		X
Pregnancy Test (women of childbearing potential only)[h]	X	X	X	X	X	X	X	X	X	X		X
HbA1c & FPG	X	X	X	X	X	X	X	X	X	X		X[u]
Lipid Panel[j]			X			X			X	X		X
Urinary Albumin/Creatinine ratio[k]			X			X			X	X		
Plasma for Future Biomedical Research[l]										X		X
Serum for Future Biomedical Research[l]										X		X
Drug												
Dispense Investigational Product	X	X	X	X	X	X	X	X	X			
Assess Compliance with Investigational Product	X	X	X	X	X	X	X	X	X	X		X
Concomitant Medications Assessment	X	X	X	X	X	X	X	X	X	X		X
Subject Education/Monitoring												
Diet/Exercise Monitoring	X	X	X	X	X	X	X	X	X	X		X
Distribute sponsor-provided glucose meter supplies.	X	X	X	X	X	X	X	X	X			
Review/Dispense Self- Monitoring Blood Glucose and Hypoglycemia Assessment Log	X	X	X	X	X	X	X	X	X	X[r]		X

Protocol Activities	Visits Following Year 1											
	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	
Months (M) Since Randomization[a]	M28	M32	M36	M40	M44	M48	M52	M56	M60[o]	ET[p]/ EOS[q]	2 Week Phone Follow Up[s]	Glycemic Rescue Visit[t]
Recommended Visit Windows	±1 month	±1 month	±1 month	±1 month	±1 month	±1 month	±1 month	±1 month	±1 month		±3 days	
Adverse Event Monitoring[p]	X	X	X	X	X	X	X	X	X	X	X	X
Potential Cardiovascular Event Assessment[q]	X	X	X	X	X	X	X	X	X	X	X	X

a. Centers should attempt to schedule each subject's visits at approximately the same time of day for that subject. The same visit schedule will be followed by all subjects enrolled in the main cardiovascular study and those enrolled in the sub-studies. Subjects should be fasting for at least 10 hours prior to visits (except water), and must be instructed to arrive **without** having taken the dose of investigational product or any other AHA (if applicable). Other medications may be administered prior to the clinic visit if they can be administered without food. On clinic visit days, subjects may eat to break their fast after the collection of weight, completion of laboratory procedures and blood pressure and pulse rate. Other AHA therapy should be administered after the subject has consumed a meal, if applicable.

b. Administer first witnessed investigational product in clinic. All Day 1 visit (V2) procedures to be completed prior to dosing unless otherwise specified.

c. Brief physical examination to include assessment of heart, lungs, abdomen, extremities and skin. Other body systems may be evaluated per the judgment of the investigator and as needed to evaluate adverse events as per Section 7.3.

d. Sitting Blood Pressure and Pulse Rate: Sitting, triplicate blood pressure and pulse rate measurement to be collected as per Section 7.7.

e. Duplicate measurements of supine and standing blood pressure and pulse rate as per Section 7.8.

f. ECG is reviewed at the investigative site for safety monitoring and submitted for central reading as per Section 7.5. If a subject experiences a non-fatal myocardial infarction after randomization, a new baseline ECG should be performed between 6 and 12 weeks following the myocardial infarction, at an unscheduled visit if necessary.

g. Routinely collected urinalysis samples will be sent to the central laboratory for dipstick analysis and microscopy if dipstick is positive for blood, nitrites, leukocytes and/or protein. Urinalysis should not be collected for a female subject who is menstruating.

h. Urine pregnancy tests will be performed for women of childbearing potential at all time points and if positive may be confirmed with a serum pregnancy test. Pregnancy tests may also be repeated at any time if requested of IRB/IECs or if required by local regulations as per Section 7.1.6.

i. Site fingerstick HbA1c is not mandatory, but may be used at the discretion of the investigator for screening subjects. However, a fingerstick HbA1c cannot substitute for a central laboratory-measured HbA1c to determine if a subject meets entry criteria.

j. Includes total cholesterol, HDL-C, LDL-C, non-HDL-C and triglycerides at all time points. If LDL-C is measured directly on a Day 1 sample, the central laboratory will perform direct LDL-C measurements on subsequent samples for that subject.

k. 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.

l. The Future Biomedical Research (FBR) informed consent must be obtained before FBR samples are drawn. The FBR sample for DNA analysis should be obtained pre-dose, at the Day 1 visit (V2) as the last sample drawn, on subjects who qualify for randomization, but 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 Day 1 (pre-dose), Week 18, Week 52 or Early Termination Visit, End of Study Visit and Glycemic Rescue Visit (if applicable). The plasma and serum samples for FBR should be collected at all time points, even if the pre-dose or other time point was not collected.

m. Assess AEs, SAEs and potential clinical events for adjudication as per Section 8.4.1 and Section 7.1.

n. Subjects will be instructed to contact the site if they are admitted to the hospital for any reason, or if they experience a cardiovascular event.

o. If the trial is deemed not complete by Visit 20 (Month 60), visits will continue on an every 4 month schedule and the list of procedures to be performed are the same as the visits for Months 52, 56 and 60 respectively until trial completion (EOS). Unscheduled visits are allowed at any time as needed for assessment of adverse events, repeat laboratory testing, etc.

p. ET = Early termination, subjects who discontinue taking investigational product prematurely but remain in the study should complete procedures for the ET visit and have a 2 week (14 days ±3 days) follow-up phone call from their last dose of investigational product. They will also be contacted via telephone by the investigator/designated representative according to the same schedule as if the subject were still taking investigational product through the end of the trial (ie, according to the Schedule of Activities and Section 6, study assessments). Subjects will be expected to attend annual visits in person. See Section 6.3.3 for additional details.

q. EOS = end of study. All EOS procedures should be performed for all randomized subjects when the trial is completed. EOS procedures should be completed whether or not the subject is taking investigational product when the trial is terminated.

r. Hypoglycemia Assessment and Blood Glucose Self-Monitoring logs will not be dispensed at ET or EOS visits.

s. Each randomized subject should have a follow-up phone call 14 days ±3 days after the last dose of investigational product to assess for SAEs (Section 8.4.1) and collect information on clinical events (Section 7.1).

t. Subjects who require glycemic rescue therapy during the first 18 weeks of the trial, as per Section 5.5.1, must have rescue therapy initiated at either a scheduled or unscheduled visit, and not by a telephone call. Rescue therapy can also be initiated by a non-study physician as described in Section 5.5.1.

u. HbA1c should not be obtained if Glycemic Rescue Visit or ET occurs within 6 weeks of randomization.

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APPENDICES

1. INTRODUCTION

1.1. Indication

Use in patients with T2DM to improve glycemic control with once daily dosing with the SGLT2 inhibitor, ertugliflozin.

1.2. Background

There has been an increase in the global prevalence of T2DM largely attributed to rising rates of excess body weight and obesity. In 2011, diabetes was estimated to affect more than 365 million people worldwide between the ages of 20-79 years and it is projected to reach more than 550 million individuals by the year 2030.[6] T2DM accounts for approximately 90-95% of all cases of diabetes. 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. 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.[7] Approximately 85% of patients with T2DM are overweight or obese, a key factor underlying the development and maintenance of insulin resistance.[8,9] Individuals with T2DM have an increased risk of developing both microvascular and macrovascular complications, including nephropathy, neuropathy, retinopathy, and cardiovascular disease. Coronary heart disease and stroke account for approximately two-thirds of deaths in people with diabetes[2] and adults with T2DM are 2 to 4 times more likely to die from cardiovascular disease than those who do not have diabetes.[1]

The sodium glucose co-transporter family (SLC5A) consists of 12 known members, including 6 gene products named SGLTs.[10] 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, 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.[11]

Ertugliflozin (MK-8835/PF-04971729) is a potent inhibitor of Sodium-Glucose co-Transporter 2 (SGLT2) and possesses a high selectivity over glucose transport via Sodium-GLucose co-Transporter 1 (SGLT1) and several other glucose transporters (GLUT1-4). Ertugliflozin inhibits renal glucose reabsorption resulting in urinary glucose excretion and thereby reducing plasma glucose and glycated hemoglobin (HbA1c) in subjects with T2DM. Ertugliflozin is being developed as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

1.2.1. Efficacy of Ertugliflozin

In Phase 2 clinical studies, subjects received ertugliflozin for up to 12 weeks in duration. Phase 2 results demonstrated that ertugliflozin significantly lowered HbA1c, 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 HbA1c (%) were observed for the 5 mg, 10 mg and 25 mg daily 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, for the 10 mg and for the 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 results for 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.

1.2.2. Safety of Ertugliflozin and SGLT2 Inhibitors

The SGLT2 inhibitors dapagliflozin, canagliflozin and empagliflozin are approved in the US and in the European Union. 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) and this adverse drug reaction was commonly reported in clinical trials with marketed SGLT2 inhibitors. Most infections were mild to moderate in severity and infections were reported more frequently in females than in males. There have also been postmarketing reports of serious UTIs including urosepsis and pyelonephritis requiring hospitalization in patients receiving marketed SGLT2 inhibitors.

SGLT2 inhibition results in an osmotic diuresis, which may lead to reductions in intravascular volume and a small decrease in blood pressure. In clinical trials with marketed SGLT2 inhibitors, treatment was associated with an increase in the incidence of adverse events related to volume depletion (eg, dehydration, hypovolemia, hypotension, orthostatic hypotension, syncope, postural dizziness). These events occurred at higher frequency and were more pronounced in some populations. As SGLT2 inhibition can lead to volume depletion, there is a concern for potential adverse renal effects. In clinical trials with marketed SGLT2 inhibitors, early declines in the estimated glomerular filtration rate (eGFR) were seen, although there was a return toward baseline levels over time during treatment and upon discontinuation of therapy. This early eGFR decline is believed to be related to dehydration and not due to progressing renal insufficiency. However, the pattern of eGFR decline appeared to be different in subjects with varying degrees of baseline renal function, with greater persistence of eGFR decline in subjects with moderate renal impairment. In addition, in subjects with moderate renal impairment there was a slightly higher incidence of renally-related adverse events reported in subjects receiving SGLT2 inhibitors than in controls.

Reports of ketoacidosis have been identified in postmarketing surveillance in patients receiving other marketed SGLT2 inhibitors. In many of these reports, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed, because blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL [13.9 mmol/L]).

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.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigators' Brochure for ertugliflozin (MK-8835/PF-04971729).

1.3. Rationale for Study

Given the substantial cardiovascular morbidity and mortality from T2DM, an understanding of the cardiac safety of a new agent for patients with T2DM is of paramount importance.

The FDA has revised its approval process and guidelines for all new anti-diabetic therapies requiring that acceptable levels of cardiovascular safety are demonstrated at the time of the NDA filing as well as post-approval.[3] The FDA guidance requires that sponsors must rule out an upper 95% CI of the HR for cardiovascular events of 1.8 before approval and 1.3 after approval.

The EMA has also updated its guidelines requiring that sponsors of novel diabetes agents exclude that the new compound increases the risk of macrovascular complications at the time of the MAA.[4] In contrast to the FDA guidance, the EMA does not specify thresholds of excess cardiovascular risk that must be excluded. Both the FDA and EMA guidance documents recommend that an assessment of cardiovascular safety needs to include subjects with T2DM and high cardiovascular risk.

The primary objective of this trial is to support the assessment of cardiovascular safety of ertugliflozin.

Additionally, after the publication of the results of the EMPA-REG OUTCOME (EMPA-REG) trial with empagliflozin,[13] a superiority analysis for the secondary end point of cardiovascular death or hospitalization for heart failure (composite) and cardiovascular death (individual) has been included in the analysis plan. In the EMPA-REG trial, which showed a significant effect in reducing the risk of MACE; HR (95% CI) 0.86 (0.74-0.99), there was also a statistically and robust reduction in cardiovascular death; HR (95% CI) 0.62 (0.49-0.77) and in hospitalization for heart failure; HR (95% CI) 0.65 (0.50-0.85), with no significant reductions in the risk of non-fatal myocardial infarction and non-fatal stroke.[13] The fact that the reduction in MACE was driven by a reduction in CV death and not non-fatal myocardial infarction or non-fatal stroke may suggest that SGLT2 inhibition might provide cardiovascular benefit from mechanisms not directly linked to an effect on atherosclerosis

per se. Therefore, while MACE is an ideal endpoint to assess cardiovascular safety, it might not be the most sensitive end point to assess the potential cardiovascular benefits of SGLT2 inhibitors. Cardiovascular death and hospitalization for heart failure are both very prevalent in the patient population enrolled in this study. Furthermore, heart failure is associated with an increased risk of mortality and has been shown to be the main cause of mortality post myocardial infarction.[14]

Subjects with T2DM and established vascular disease comprise a large segment of the population which would be treated with an SGLT2 inhibitor. Such subjects are often underrepresented in clinical trials which limits their ability to provide meaningful information on the benefit:risk profile of novel agents in an important population. Therefore, this trial will enroll subjects with T2DM who are at elevated risk of cardiovascular events. The population enrolled in this trial is, therefore, representative of those subjects often treated in clinical practice, with T2DM and elevated risk of cardiovascular disease.

Additionally, this trial includes a sub-study to generate safety and efficacy data in subjects using insulin with or without metformin, a sub-study to generate safety and efficacy data in subjects using SU monotherapy and another sub-study to generate safety and efficacy data in subjects using metformin with SU.

While the subjects in the placebo arm in this trial will not receive active treatment with ertugliflozin, they will be counseled on life style measures to attain improved glycemic control and for all subjects in the trial (either on placebo or ertugliflozin), following the initial 18 weeks of the trial, the investigator or subject´s treating physician is able to make any necessary adjustments in background diabetes medications to achieve appropriate, individualized treatment goals. Furthermore, as described in Section 5.5.2 all subjects in the trial will continue to receive treatment to address cardiovascular risk factors (eg, blood pressure management, lipid management).

1.4. Rationale for Dose Selection of Ertugliflozin

The ertugliflozin doses being evaluated in Phase 3 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 (HbA1c and fasting plasma glucose [FPG]) from study B1521006 as well as 24-hour urinary glucose excretion (mechanism biomarker) in T2DM subjects from study B1521004. For these endpoints, the 5 mg and 15 mg doses consistently elicit a response that is >80% and >90% of the maximum response, respectively (Table 1).

Table 1. Estimated Percent Maximum Response for Various Endpoints

Ertugliflozin Dose	UGE – T2DM (ED_{50}=0.78 mg)	HbA1C (ED_{50}=1 mg)
5 mg	87%	83%
15 mg	95%	94%

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 3 dose of 15 mg once daily represents an exposure which is approximately 12-fold [for C_{max}] and 11-fold [for area under the concentration-time curve from time 0 to 24 hours (1 day) after dose ($AUC_{(0-24)}$)] 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 3 program.

1.5. Rationale for Future Biomedical Research

The sponsor will conduct Future Biomedical Research on whole blood DNA, plasma and serum 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. Specimens may be used for future assay development. 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 pharmacogenetics (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, and/or to ensure that subjects receive the correct dose of the correct drug at the correct time. The details of this Future Biomedical Research sub-trial are presented in Appendix 1: 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 Appendix 2.

2. STUDY OBJECTIVES, HYPOTHESES AND ENDPOINTS

2.1. Objectives and Hypotheses

2.1.1. Primary Objective and Hypothesis

- **Objective:** To demonstrate the non-inferiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of MACE. (MACE: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke)

- **Hypothesis:** The time to first occurrence of the composite endpoint of MACE in subjects treated with ertugliflozin is non-inferior compared to that in subjects treated with placebo.

2.1.2. Secondary Objectives and Hypotheses

- **Objective**: To demonstrate the superiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of cardiovascular death or hospitalization for heart failure.

- **Hypothesis**: The time to first occurrence of the composite endpoint of cardiovascular death or hospitalization for heart failure in subjects treated with ertugliflozin is superior compared to that in subjects treated with placebo.

- **Objective**: To demonstrate the superiority of ertugliflozin compared with placebo on the time to cardiovascular death.

- **Hypothesis**: The time to cardiovascular death in subjects treated with ertugliflozin is superior compared to that in subjects treated with placebo.

- **Objective**: To demonstrate the superiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of renal death, renal dialysis/transplant, or ≥2x increase in baseline serum creatinine.

- **Hypothesis**: The time to first occurrence of the composite endpoint of renal death, renal dialysis/transplant, or ≥2x increase in baseline serum creatinine in subjects treated with ertugliflozin is superior compared to that in subjects treated with placebo.

- **Objective:** To assess the effect of ertugliflozin as compared with placebo on the time to first occurrence of:

  - MACE plus;

  - Fatal or non-fatal myocardial infarction;

  - Fatal or non-fatal stroke;

  - Hospitalization for heart failure;

  - Individual components of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke).

- **Objective:** To assess the effect of ertugliflozin as compared with placebo on the time to:

  - All-cause mortality;

- All MACE events (not censored at time of first event);
- All cardiovascular death or hospitalizations for heart failure (not censored at time of first event).

When added to usual background therapy in subjects with T2DM and established vascular disease:

- **Objective:** To assess the overall safety and tolerability of ertugliflozin.
- **Objective:** To assess the effect on HbA1c of 15 mg ertugliflozin as compared with placebo.
- **Objective:** To assess the effect on HbA1c of 5 mg ertugliflozin as compared with placebo.
- **Objective:** To assess the effect on FPG of 15 mg ertugliflozin as compared with placebo.
- **Objective:** To assess the effect on FPG of 5 mg ertugliflozin as compared with placebo.
- **Objective:** To assess the effect on time to first occurrence of a subject requiring glycemic rescue therapy during the first 18 weeks of 15 mg ertugliflozin as compared with placebo.
- **Objective:** To assess the effect on time to first occurrence of a subject requiring glycemic rescue therapy during the first 18 weeks of 5 mg ertugliflozin as compared with placebo.
- **Objective:** To assess the effect on the time to initiation of insulin for subjects not on insulin at randomization of 15 mg ertugliflozin as compared with placebo.
- **Objective:** To assess the effect on the time to initiation of insulin for subjects not on insulin at randomization of 5 mg ertugliflozin as compared with placebo.
- **Objective:** To assess the change in insulin dose over time for subjects receiving insulin at the time of randomization of 15 mg ertugliflozin as compared with placebo.
- **Objective:** To assess the change in insulin dose over time for subjects receiving insulin at the time of randomization of 5 mg ertugliflozin as compared with placebo
- **Objective:** To assess the effect on body weight of 15 mg ertugliflozin as compared with placebo.
- **Objective:** To assess the effect on body weight of 5 mg ertugliflozin as compared with placebo.

- **Objective:** To assess the effect on the incidence of HbA1c <7% (53 mmol/mol) of 15 mg ertugliflozin as compared with placebo.

- **Objective:** To assess the effect on the incidence of HbA1c <7% (53 mmol/mol) of 5 mg ertugliflozin as compared with placebo.

- **Objective:** To assess the effect on the incidence of HbA1c of <6.5% (48 mmol/mol) of 15 mg ertugliflozin as compared with placebo.

- **Objective:** To assess the effect on the incidence of HbA1c <6.5% (48 mmol/mol) of 5 mg ertugliflozin as compared with placebo.

- **Objective:** To assess the effect on systolic blood pressure of 15 mg ertugliflozin as compared with placebo.

- **Objective:** To assess the effect on systolic blood pressure of 5 mg ertugliflozin as compared with placebo.

- **Objective:** To assess the effect on diastolic blood pressure of 15 mg ertugliflozin as compared with placebo.

- **Objective:** To assess the effect on diastolic blood pressure of 5 mg ertugliflozin as compared with placebo.

- **Objective:** To assess the effect on renal function of 15 mg ertugliflozin as compared with placebo.

- **Objective:** To assess the effect on renal function of 5 mg ertugliflozin as compared with placebo.

2.2. Insulin with or without Metformin Add-on Glycemic Sub-Study Objectives and Hypotheses

In subjects with T2DM and established vascular disease with inadequate glycemic control receiving only insulin (with or without metformin):

2.2.1. Primary Objectives and Hypotheses

- Objective: At Week 18, to assess the effect on HbA1c of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in HbA1c for 15 mg ertugliflozin is greater than that for placebo.

- **Objective**: At Week 18, to assess the effect on HbA1c of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in HbA1c for 5 mg ertugliflozin is greater than that for placebo.

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

2.2.2. Secondary Objectives and Hypotheses

- **Objective:** At Week 18, to assess the effect on FPG of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in FPG for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on FPG of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in FPG for 5 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on body weight of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in body weight for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on body weight of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in body weight for 5 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on the incidence of HbA1c <7% (53 mmol/mol) of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis**: At Week 18, the proportion of subjects with HbA1c<7% (53 mmol/mol) for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on incidence of HbA1c <7% (53 mmol/mol) of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis**: At Week 18, the proportion of subjects with HbA1c<7% (53 mmol/mol) for 5 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on systolic blood pressure of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in systolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on systolic blood pressure of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in systolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18 to assess the effect on diastolic blood pressure of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in diastolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on diastolic blood pressure of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in diastolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the change in insulin dose of 15 mg ertugliflozin as compared with placebo.

- **Objective:** At Week 18, to assess the change in insulin dose of 5 mg with ertugliflozin as compared with placebo.

2.3. SU Monotherapy Add-on Glycemic Sub-Study Objectives and Hypotheses

In subjects with T2DM and established vascular disease with inadequate glycemic control on SU monotherapy:

2.3.1. Primary Objectives and Hypotheses

- **Objective:** At Week 18, to assess the effect on HbA1c of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in HbA1c for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on HbA1c of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in HbA1c for 5 mg ertugliflozin is greater than that for placebo

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

2.3.2. Secondary Objectives and Hypotheses

- **Objective:** At Week 18, to assess the effect on FPG of 15 mg ertugliflozin as compared with placebo.
- **Hypothesis:** At Week 18, the mean reduction from baseline in FPG for 15 mg ertugliflozin is greater than that for placebo.
- **Objective:** At Week 18, to assess the effect on FPG of 5 mg ertugliflozin as compared with placebo.
- **Hypothesis:** At Week 18, the mean reduction from baseline in FPG for 5 mg ertugliflozin is greater than that for placebo.
- **Objective:** At Week 18, to assess the effect on body weight of 15 mg ertugliflozin as compared with placebo.
- **Hypothesis:** At Week 18, the mean reduction from baseline in body weight for 15 mg ertugliflozin is greater than that for placebo
- **Objective:** At Week 18, to assess the effect on body weight of 5 mg ertugliflozin as compared with placebo.
- **Hypothesis:** At Week 18, the mean reduction from baseline in body weight for 5 mg ertugliflozin is greater than that for placebo.
- **Objective:** At Week 18, to assess the effect on the incidence of HbA1c <7% (53 mmol/mol) of 15 mg ertugliflozin as compared with placebo.
- **Hypothesis**: At Week 18, the proportion of subjects with HbA1c<7% (53 mmol/mol) for 15 mg ertugliflozin is greater than that for placebo.
- **Objective:** At Week 18, to assess the effect on the incidence of HbA1c <7% (53 mmol/mol) of 5 mg ertugliflozin as compared with placebo.
- **Hypothesis**: At Week 18, the proportion of subjects with HbA1c<7% (53 mmol/mol) for 5 mg ertugliflozin is greater than that for placebo.
- **Objective:** At Week 18, to assess the effect on systolic blood pressure of 15 mg ertugliflozin as compared with placebo.
- **Hypothesis:** At Week 18, the mean reduction from baseline in systolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.
- **Objective:** At Week 18, to assess the effect on systolic blood pressure of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in systolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18 to assess the effect on diastolic blood pressure of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in diastolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on diastolic blood pressure of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in diastolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

2.4. Metformin with SU Add-on Glycemic Sub-Study Objectives and Hypotheses

In subjects with T2DM and established vascular disease with inadequate glycemic control receiving only metformin with SU:

2.4.1. Primary Objectives and Hypotheses

- **Objective:** At Week 18, to assess the effect on HbA1c of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in HbA1c for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on HbA1c of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in HbA1c for 5 mg ertugliflozin is greater than that for placebo.

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

2.4.2. Secondary Objectives and Hypotheses

- **Objective:** At Week 18, to assess the effect on FPG of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in FPG for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on FPG of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in FPG for 5 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on body weight of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in body weight for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on body weight of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in body weight for 5 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on the incidence of HbA1c <7% (53 mmol/mol) of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis**: At Week 18, the proportion of subjects with HbA1c<7% (53 mmol/mol) for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on incidence of HbA1c <7% (53 mmol/mol) of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis**: At Week 18, the proportion of subjects with HbA1c<7% (53 mmol/mol) for 5 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on systolic blood pressure of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in systolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on systolic blood pressure of 5 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in systolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18 to assess the effect on diastolic blood pressure of 15 mg ertugliflozin as compared with placebo.

- **Hypothesis:** At Week 18, the mean reduction from baseline in diastolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

- **Objective:** At Week 18, to assess the effect on diastolic blood pressure of 5 mg ertugliflozin as compared with placebo.

- Hypothesis: At Week 18, the mean reduction from baseline in diastolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

2.5. Objective and Hypothesis Across the Ertugliflozin Phase 2 and Phase 3 Development Program

- **Objective:** To demonstrate the non-inferiority of ertugliflozin as compared with a non-ertugliflozin comparator group on the time to first occurrence of the composite endpoint of MACE plus.

- **Hypothesis:** The time to first occurrence of the composite endpoint of MACE plus in subjects treated with ertugliflozin is non-inferior compared to that in subjects not treated with ertugliflozin.

Further details regarding the meta-analysis across the Ertugliflozin Phase 2 and Phase 3 Development Program are provided in the Statistical Analysis Plan (SAP) document.

2.6. Study Endpoints

All potential cardiovascular endpoints across the ertugliflozin Phase 2 and Phase 3 development program are to be adjudicated by members of an independent Endpoint Adjudication Committee (EAC) who will be blinded to the treatment assignment. Endpoint definitions will be included in the Endpoint Adjudication Manual used by the EAC. Only adjudicated and confirmed endpoints will be used in the analysis of the cardiovascular event data.

2.6.1. Primary Endpoint

- The primary cardiovascular endpoint is time to first occurrence of the composite endpoint of MACE.

2.6.2. Secondary Endpoints

- Time to first occurrence of:
  - Cardiovascular death or hospitalization for heart failure;
  - Cardiovascular death;
  - MACE plus;
  - Fatal or non-fatal myocardial infarction;
  - Fatal or non-fatal stroke;
  - Hospitalization for heart failure;
  - Individual components of MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke).

- All-cause mortality.
- All MACE events (ie, not censored at the time of the first event).
- All cardiovascular death or hospitalizations for heart failure (ie, not censored at the time of the first event).
- Time to first occurrence of the composite of renal death, renal dialysis/transplant, or ≥2x increase in baseline serum creatinine.

When added to usual background therapy in subjects with T2DM and established vascular disease:

- Change from Baseline in HbA1c at Week 18, Week 52 and annually thereafter.
- Proportion of subjects with HbA1c <7% (53 mmol/mol) and <6.5% (48 mmol/mol) at 12, 24 and 36 months and annually thereafter.
- Time to the first occurrence of a subject receiving glycemic rescue therapy during the first 18 weeks of the study.
- Time to initiation of insulin for subjects not on insulin at randomization.
- Change in insulin dose from Baseline at Week 18, Week 52 and annually thereafter.
- Change from Baseline in systolic and diastolic blood pressure at Week 18, Week 52 and annually thereafter.
- Change from Baseline in body weight at Week 18, Week 52 and annually thereafter.
- Change from Baseline in eGFR and serum creatinine at Week 18, Week 52 and annually thereafter.
- Change from Baseline in albuminuria as measured by the urinary albumin to creatinine ratio at Week 18, Week 52 and annually thereafter stratified by albuminuria category at baseline (normoalbuminuria, microalbuminuria and macroalbuminuria).
- Progression of nephropathy as measured by the progression of normoalbuminuria to microalbuminuria and/or macroalbuminuria as well as measurement of regression of albuminuria (eg, macroalbuminuria → microalbuminuria).

2.7. Insulin with or without Metformin Add-on Glycemic Sub-Study Endpoints

2.7.1. Primary Endpoint

- Change in HbA1c from Baseline to Week 18.

2.7.2. Secondary Endpoints

- Change in FPG from Baseline to Week 18.
- Change in body weight from Baseline to Week 18.
- Proportion of subjects with an HbA1c of <7% (53 mmol/mol) at Week 18.
- Change in systolic and diastolic blood pressure from Baseline to Week 18.
- Change in insulin dose from Baseline to Week 18.

2.8. SU Monotherapy Add-on Glycemic Sub-Study Endpoints

2.8.1. Primary Endpoint

- Change in HbA1c from Baseline to Week 18.

2.8.2. Secondary Endpoints

- Change in FPG from Baseline to Week 18.
- Change in body weight from Baseline to Week 18.
- Proportion of subjects with an HbA1c of <7% (53 mmol/mol) at Week 18.
- Change in systolic and diastolic blood pressure from Baseline to Week 18.

2.9. Metformin with SU Add-on Glycemic Sub-Study Endpoints

2.9.1. Primary Endpoint

- Change in HbA1c from Baseline to Week 18.

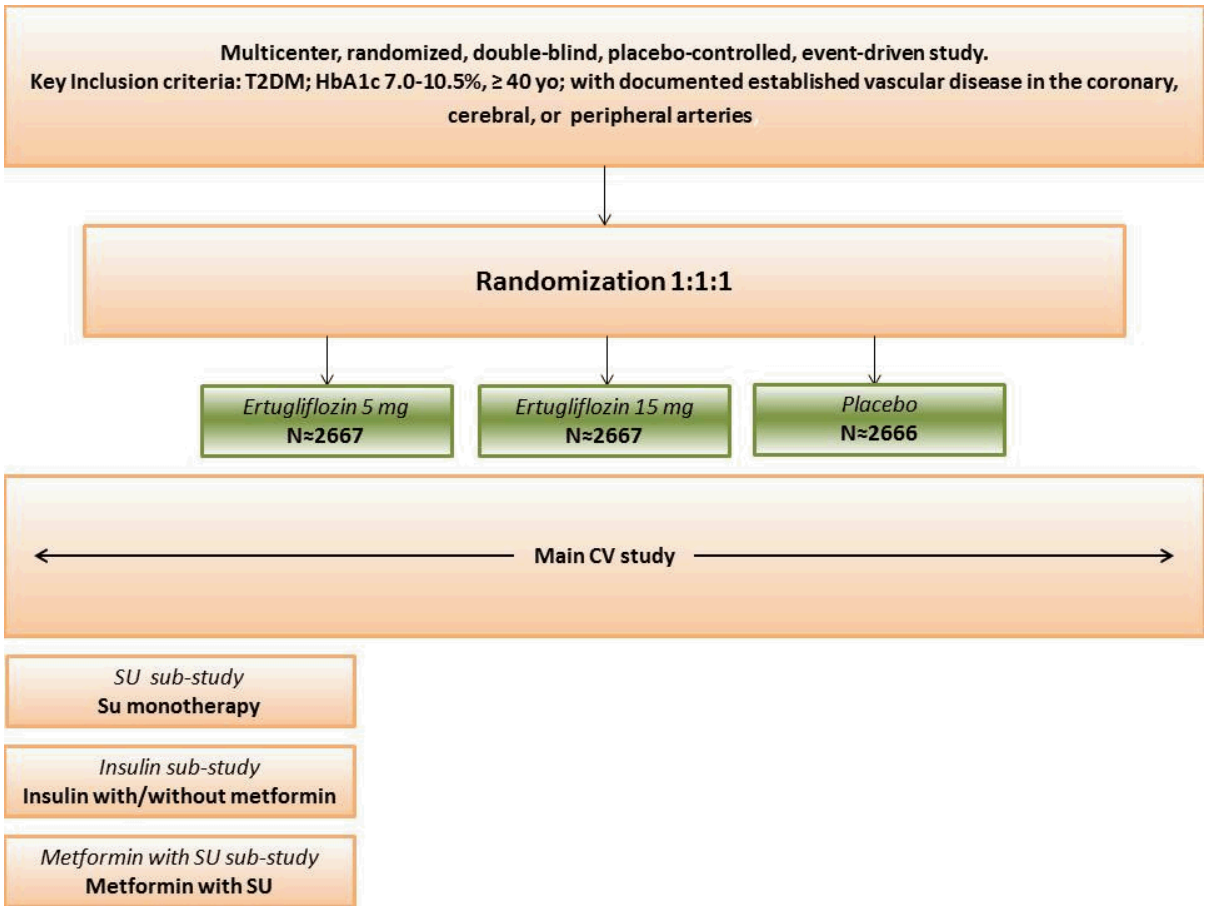
2.9.2. Secondary Endpoints

- Change in FPG from Baseline to Week 18.
- Change in body weight from Baseline to Week 18.
- Proportion of subjects with an HbA1c of <7% (53 mmol/mol) at Week 18.
- Change in systolic and diastolic blood pressure from Baseline to Week 18.

2.10. Endpoint Across the Ertugliflozin Phase 2 and Phase 3 Development Program

- Time to first occurrence of the composite endpoint of MACE plus.

3. STUDY DESIGN



3.1. Overview of Study Design (Main Cardiovascular Study and add-on Glycemic Sub-Studies)

This trial is a multicenter, randomized, double-blind, placebo-controlled, event-driven trial that includes a main cardiovascular study and three add-on glycemic sub-studies in subjects receiving specific background anti-hyperglycemic treatments. Periodic assessments of safety will be performed by an external Data Monitoring Committee (E-DMC). Further details are provided in Section 9.9.

To be enrolled in this trial subjects must be ≥40 years of age with a previous diagnosis of T2DM in accordance with ADA guidelines,[5] HbA1c of 7.0-10.5%, inclusive (53-91 mmol/mol) and a history of established vascular disease involving the coronary, cerebrovascular, or peripheral vascular system. Subjects who are treated with oral anti-hyperglycemic agents (AHA), insulin or GLP-1 agonists, either alone or in combination, stable for at least 8 weeks prior to the Screening visit (V1) or subjects who are on only diet and exercise for T2DM are eligible to be enrolled. Background AHA treatment must continue to remain stable throughout the length of the Screening period. The only prohibited concomitant AHA therapy is the use of any other SGLT2 therapy (eg, dapagliflozin, canagliflozin, empagliflozin, etc.), rosiglitazone or chlorpropamide within 8 weeks of the

Screening visit (V1), between the screening period and randomization or during the trial. Other key exclusion criteria include subjects with an eGFR <30 mL/min/1.73 m^2, see for further details. Full inclusion and exclusion criteria are found in Section 4.2. Specific criteria for inclusion in the glycemic sub-studies are detailed in Sections 3.4, 4.1.1, 4.1.2, 4.2.1. Subjects will be screened for eligibility at the Screening visit (V1). At the Day 1 visit (V2), subjects who meet all 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 once daily, ertugliflozin 15 mg once daily or matching placebo added to their background therapy.

This trial will contribute to the program-wide meta-analysis of cardiovascular events occurring in the ertugliflozin Phase 2 and Phase 3 development program as follows.

For the initial global registration dossiers (including the NDA submission), the cardiovascular events from this trial will be combined with the cardiovascular events from the rest of the Phase 2 and Phase 3 development program to conduct a program-wide meta-analysis to support the cardiovascular safety of ertugliflozin. The endpoint for this meta-analysis will be MACE plus. The goal of this meta-analysis will be to rule out a hazard ratio of 1.8 (an 80% increase in the risk of MACE plus relative to a non-ertugliflozin comparator group) by showing that the upper bound of the two-sided alpha-adjusted confidence interval for the hazard ratio is <1.8.

The primary cardiovascular endpoint for this study will be MACE. The goal of this analysis is to rule out a hazard ratio of 1.3 (a 30% increase in the risk of MACE relative to placebo).

If non-inferiority at the 1.3 margin is established for the primary MACE endpoint, then tests of superiority on the secondary endpoints of cardiovascular death or hospitalization for heart failure (composite) and cardiovascular death (individual component) will also be performed.

The trial will utilize a group sequential design that includes interim analyses. With two enrollment periods of 19 months each and assuming an event rate of 3.5% per annum for MACE, a total of approximately 8000 subjects randomized in a 1:1:1 ratio to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo will be sufficient to accrue approximately 714 MACE events within approximately 5.0 years and approximately 939 MACE events within approximately 6.1 years from the start of this trial. These calculations assume that subjects will withdraw from the study at a rate of 5% per annum.

All randomized subjects will be followed until the scheduled end of the trial regardless of adherence to or discontinuation of investigational product unless a subject withdraws consent for follow-up. This follow-up will be undertaken so that information on SAEs and clinical events continues to be collected. Further details are provided in Section 6.6.

All subjects enrolled under the original protocol prior to Amendment 1 will be randomized into the overall study, and subjects meeting additional inclusion criteria will also be included in specific glycemic sub-studies. Subjects enrolled after the approval of Amendment 1 will only be randomized into the overall study. For these subjects, the protocol sub-study details described below and in Sections 4.1.1, 4.1.2, and 4.2.1 are not applicable. At the time of randomization, subjects in Cohort 1 will be stratified into the main cardiovascular study, the

insulin (with or with metformin) sub-study or the SU monotherapy sub-study, according to their background anti-hyperglycemic treatment as follows. Subjects receiving background insulin (with or without metformin) at doses specified in the protocol are included into the insulin (with or without metformin) add-on glycemic sub-study, subjects receiving background SU monotherapy (at doses specified in the protocol) are included into the SU monotherapy add-on glycemic sub-study. Subjects receiving background metformin with SU at doses specified in the protocol are included in the metformin plus SU sub-study. Unlike the other two sub-studies, inclusion in the metformin with SU sub-study will not be stratified at randomization. Instead, all subjects randomized into the main cardiovascular study who meet the additional eligibility requirements will be considered enrolled in this sub-study. Since all the subjects participating in the three sub-studies are enrolled in the main cardiovascular study, visit schedules and protocol-required tests and procedures are the same for all subjects irrespective of whether or not a subject also participates in a sub study. The glycemic sub-studies will run during the initial 18 weeks of the study. Following the collection of efficacy and safety end points at Week 18 (V5), subjects in the glycemic sub-studies will continue participating in the main cardiovascular study.

3.2. Insulin with or without Metformin Add-on Glycemic Sub-Study

This trial includes an 18-week sub-study to generate safety and efficacy data in T2DM subjects using insulin therapy alone or insulin with metformin as the only background anti-hyperglycemic treatment. The insulin with or without metformin sub-study has different requirements with respect to allowable background AHA than the main cardiovascular study.

Subjects are entered into the sub-study if they are using insulin ≥20 units/day (with or without metformin ≥1,500 mg/day) as the only background anti-hyperglycemic treatment. Subjects can be on basal insulin alone (eg, insulin glargine, insulin detemir, Neutral Protamine Hagedorn (NPH) insulin, degludec), split mixed insulin (eg, 70/30) or basal insulin + prandial insulin (eg, regular, aspart, lispro or glulisine). Subjects receiving prandial insulin as their only insulin regimen, without basal insulin, are not eligible for enrollment into the sub-study. Insulin total daily dose variations of up to ±10% during the 8 weeks prior to the Screening visit (V1) or during the period between the Screening visit (V1) and randomization are permitted and fulfill the criterion of stable insulin therapy. It is recommended that the daily dose variations are compared to the average weekly dose to account for day-to-day variability. Further details on the inclusion criteria for the insulin with or without metformin sub-study can be found in Section 4.1.1.

Subjects eligible for the main cardiovascular study using insulin with any diabetes regimen other than insulin with or without metformin ≥1,500 mg/day or subjects not meeting the insulin type and dose requirements as specified in the inclusion criteria will be enrolled in the main study, but not in the sub-study. Further details on the exclusion criteria for the insulin with or without metformin sub-study can be found in Section 4.2.1.

This insulin with or without metformin sub-study plans to enroll a minimum of 450 subjects who will be randomized in a 1:1:1 ratio to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo. The sub-study randomization will be stratified by background therapy and geographic region. The background therapy stratification factor will have two levels: insulin alone and insulin

with metformin. The number of subjects using background insulin in the overall study population enrolled in this trial will not be allowed to exceed approximately 50%. The primary endpoint of HbA1c change from Baseline will be measured at Week 18. Secondary endpoints include change from Baseline in FPG, body weight, the proportion of subjects with an HbA1c <7% (53 mmol/mol) at Week 18, change from Baseline in systolic and diastolic blood pressure at Week 18 and change from Baseline in insulin dose at Week 18. Details on the treatment for glycemic control can be found in Section 5.5.1. After Week 18 subjects enrolled in the insulin with or without metformin sub-study will continue to participate in the main cardiovascular study.

3.3. SU Monotherapy Add-on Glycemic Sub-Study

This trial includes an 18-week sub-study to generate safety and efficacy data in subjects using a SU as monotherapy at the pre-specified doses specified in Table 2 in Section 4.1.2. The SU monotherapy sub-study has different requirements with respect to allowable background AHA than the main cardiovascular study. Further details on the inclusion criteria for the SU monotherapy sub-study can be found in Section 4.1.2.

Subjects receiving a SU eligible to participate in the main study at a dose less than that specified in Table 2 could still be enrolled in the main cardiovascular study but not in the sub-study.

Based on the percentage of subjects receiving treatment with SU monotherapy enrolled in a similar trial, the CANVAS study (approximately 3% of the total population)[12] it is estimated that approximately 120 subjects will be enrolled in the SU monotherapy sub-study and they will be randomized in a 1:1:1 ratio to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo. There is no maximum number of subjects who can be enrolled in the sub-study on SU monotherapy.

The primary endpoint of HbA1c change from Baseline will be measured at Week 18. Secondary endpoints include change from Baseline in FPG, body weight, the proportion of subjects with an HbA1c <7% (53 mmol/mol) at Week 18 and change from Baseline in systolic and diastolic blood pressure at Week 18. Details on the treatment for glycemic control can be found in Section 5.5.1. After Week 18 subjects enrolled in the SU monotherapy sub-study will continue to participate in the main cardiovascular study.

3.4. Metformin with SU Add-on Glycemic Sub-Study

This trial includes an 18-week sub-study to generate safety and efficacy data in T2DM subjects using metformin with a SU as the only background anti-hyperglycemic treatment. The metformin with SU sub-study has different requirements with respect to allowable background AHA than the main cardiovascular study.

Subjects will be included in this sub-study if they are receiving at the Screening visit (V1) metformin ≥1500 mg/day with a SU at the doses specified in Table 2 in Section 4.1.2. The doses of the metformin and SU must have been stable for at least 8 weeks prior to the time of the Screening visit (V1) and during the period between the Screening visit (V1) and randomization. Subjects will not be included in the metformin with SU sub-study if their

screening eGFR is <55 mL/min/1.73m^2 or the screening serum creatinine is ≥1.3 mg/dL (115 μmol/l) in males or ≥1.2 mg/dL (110 μmol/l) in females. These renal entry criteria were selected as they match the renal entry criteria used throughout the ertugliflozin program for studies where metformin is a required background treatment.

As there is no separate randomization stratum for the metformin with SU sub-study, this sub-study will consist of a sub-group of subjects from the "main cardiovascular study" stratum. The determination of inclusion in the sub-study will be based on a programmatic assessment of the sub-study criteria.

The primary endpoint of HbA1c change from Baseline will be measured at Week 18. Secondary endpoints include change from Baseline in FPG, body weight, the proportion of subjects with an HbA1c <7% (53 mmol/mol) at Week 18 and change from Baseline in systolic and diastolic blood pressure at Week 18. Details on the treatment for glycemic control can be found in Section 5.5.1.

4. SUBJECT SELECTION

This trial can fulfill its objectives only if appropriate subjects are enrolled and followed throughout the completion of the trial irrespective of whether they are maintained on investigational product. All efforts should be made to follow randomized subjects for the entire duration of the study. Importantly, discontinuation of investigational product does not imply or constitute withdrawal of the subject from the study. Section 6.6 describes the follow-up procedures for subjects who withdraw from investigational product. In general, investigators should try to obtain the most complete collection of data as possible from subjects who discontinue investigational product, weighing the subject's willingness to participate with the scientific integrity of the protocol. Those subjects who are *a priori* unwilling to agree to the collection of the information in the event that they discontinue investigational product should not be enrolled.

The following eligibility criteria are designed to select subjects for whom protocol-specified treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's trial team before subjects are included in the trial. Subjects must meet all of the following inclusion criteria at the time of the Screening visit (V1) to be eligible for enrollment into the trial:

1. Subjects ≥40 years of age at the time of the initial Screening visit (V1) with a diagnosis of T2DM in accordance with American Diabetes Association (ADA) guidelines.[5]

2. HbA1c at the Screening visit (V1) of 7.0-10.5% (53-91 mmol/mol) on stable allowable AHA(s) or on no background AHA for at least 8 weeks prior to the Screening visit (V1).

3. Body Mass Index (BMI) ≥18.0 kg/m^2.

4. Subjects must have evidence or a history of atherosclerosis involving the coronary, cerebral or peripheral vascular systems as follows **(must have at least one of the following a-d):**

    a. Coronary artery disease as indicated by a history of presumed spontaneous myocardial infarction (hospitalized with final diagnosis of myocardial infarction, excluding peri-procedural or definite secondary myocardial infarction [eg, due to profound anemia or hypertensive emergency, troponin increase in sepsis] in which the most recent event occurred at least 3 months (90 days) prior to the Screening visit (V1); **OR**

    b. Coronary artery disease as indicated by a history of coronary revascularization through either a Percutaneous Coronary Intervention (PCI) at least 3 months (90 days) prior to the Screening visit (V1) or Coronary Artery Bypass Graft (CABG) at least 3 months (90 days) prior to the Screening visit (V1); **OR**

    c. Ischemic (presumed thrombotic) cerebrovascular disease as indicated by a history of ischemic stroke (hospitalized with a final diagnosis of non-hemorrhagic stroke [includes completion of a standard evaluation for stroke in an acute care facility or stroke clinic without hospital admission] with the most recent event occurring at least 3 months (90 days) prior to the Screening visit (V1) or a history of carotid revascularization at least 3 months (90 days) prior to the Screening visit (V1); OR

    d. Peripheral arterial disease as indicated by:

        1. Angiographically-documented peripheral vascular disease; **or**

        2. Resting ankle/brachial index (ABI) of <0.85 (measured by a certified vascular laboratory) plus symptoms of claudication; **or**

        3. Amputation, peripheral bypass, or peripheral angioplasty of the extremities secondary to ischemia occurring at least 3 months (90 days) prior to the Screening visit (V1).

5. There is adequate documentation of the objective evidence that the subject has established vascular disease such as investigational site's medical records, copies of such records from other institutions, or a letter from a referring physician that specifically states the diagnosis and date of the most recent occurrence of the qualifying event(s) or procedure(s).

6. Subject meets one of the following criteria (a, b or c):

    a. Is a male;

b. Is a female not of reproductive potential defined as one who (See Section 4.4.4.1 and Section 4.4.4.2 for reference on childbearing potential):

   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 the Screening visit (V1).

c. 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); or

   2. Agrees to use (or have their partner use) acceptable contraception to prevent pregnancy while the subject is receiving investigational product and for 14 days after the last dose of 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 intrauterine device (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).

7. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject (or a legal representative) 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.

8. In the investigator's opinion subjects are willing and likely able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures whether or not they receive investigational product for the duration of the trial.

4.1.1. Inclusion Criteria – Specific to Insulin with or without Metformin Add-on Glycemic Sub-Study

In addition to meeting the above mentioned inclusion criteria for enrollment in the main cardiovascular study, subjects will be eligible to be enrolled in this sub-study if they meet the following additional entry criteria at the time of the Screening visit (V1):

9. Insulin ≥20 units/day with or without metformin ≥1,500 mg/day, where doses of insulin with or without metformin have been stable for at least 8 weeks prior to the time of the Screening visit (V1) and during the period between the Screening visit (V1) and randomization. Variations in the total daily dose of insulin of up to 10% are permitted and still meet the definition of stable insulin dose.

4.1.2. Inclusion Criteria – Specific to SU Monotherapy Add-on Glycemic Sub-Study

In addition to meeting the above mentioned inclusion criteria for enrollment in the main cardiovascular study, subjects will be eligible to be enrolled in this sub-study if they meet the following additional entry criteria at the time of the Screening visit (V1):

10. Monotherapy with a SU at the doses specified in Table 2. The dose of the SU monotherapy must have been stable for at least 8 weeks prior to the time of the Screening visit (V1) and during the period between the Screening visit (V1) and randomization.

Table 2. Minimum Daily Doses of SU for Entry into Sub-Studies

Drug	Minimum Daily Doses of SU
Glyburide (Glibenclamide)	≥10 mg
Micronized Glyburide	≥6 mg
Glipizide	≥10 mg
Gliclazide (immediate-release)	≥160 mg
Gliclazide (modified-release)	≥60 mg
Glimepiride	≥4 mg
Acetohexamide	≥750 mg
Tolbutamide	≥1500 mg
Tolazamide	≥500 mg

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the trial:

1. Subjects who had been previously randomized into this trial.

2. Subjects experiencing a cardiovascular event (eg, myocardial infarction or stroke) or undergoing coronary angioplasty or peripheral intervention procedure between the Screening visit (V1) and randomization.

3. Subjects undergoing any cardiovascular surgery (eg, valvular surgery) within 3 months (90 days) of the Screening visit (V1).

4. Subjects with any planned coronary revascularization or peripheral intervention procedure or other cardiovascular surgery.

5. Subjects with New York Heart Association (NYHA) Class IV heart failure at the Screening visit (V1).

6. Mean value for triplicate screening sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg after at least a 5-minute seated rest at the Screening visit (V1), confirmed via 1 repeat triplicate set at the Screening visit (V1) if deemed necessary. For subjects with a mean triplicate value of sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg after at least a 5-minute seated rest at the Screening visit (V1) the investigator or the treating physician is allowed to adjust background blood pressure medication(s) to lower blood pressure values in order for the subject to be re-assessed for enrollment eligibility.

7. Subject has a clinically significant electrocardiogram (ECG) abnormality at Screening visit (V1) that requires further diagnostic evaluation or intervention (eg, new, clinically significant arrhythmia or a conduction disturbance).

8. History of type 1 diabetes mellitus or a history of ketoacidosis.

9. History of other specific types of diabetes (eg, genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant).

10. Subject has active, obstructive uropathy or indwelling urinary catheter.

11. Subject has a history of malignancy ≤5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

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

    Note (2) A subject with any history of melanoma, leukemia, lymphoma, or renal cell carcinoma is excluded.

12. Subject 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.

13. Any clinically significant malabsorption condition.

14. Subjects with a known hypersensitivity or intolerance to any SGLT2 inhibitor.

15. Screening fasting plasma or finger-stick glucose >270 mg/dL (15 mmol/L), confirmed by a single repeat following counseling on exercise and diet.

16. History of one or more severe hypoglycemic episodes within 6 months of Screening (V1) or a severe hypoglycemic episode occurring during the interval between the Screening visit (V1) and randomization.

17. Fasting triglycerides >600 mg/dL (6.78 mmol/L) at Screening (V1), confirmed by a single repeat if deemed necessary. For subjects with fasting triglycerides >600 mg/dL the investigator or treating physician is allowed to adjust background lipid altering medication(s) to lower fasting triglycerides in order for the subject to be re-assessed for enrollment eligibility.

18. Subjects currently taking blood pressure or lipid altering medications that have not been on a stable dose for at least 4 weeks prior to randomization. Subjects who require a change in blood pressure and/or lipid altering medications to meet the entry criteria related to blood pressure and/or triglycerides must be on a stable dose of such therapy for at least 4 weeks prior to randomization.

19. Subjects who meet any of the following categories:

    - Subject is on a weight-loss program and is not weight-stable.
    - Subject is on a weight-loss medication (eg, orlistat, phentermine/topiramate, lorcaserin) and is not weight-stable.
    - Subject is on other medications associated with weight changes (eg, 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 Screening visit (Visit 1).

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

20. Subjects currently being treated for hyperthyroidism, subjects on thyroid replacement therapy that have not been on a stable dose for at least 6 weeks prior to the Screening visit (V1) and/or subjects who have a thyroid stimulating hormone (TSH) outside of the laboratory reference range at the Screening visit (V1). Subjects excluded due to TSH criterion may be re-tested after being on a stable thyroid replacement regimen for at least 6 weeks.

21. eGFR <30 mL/min/1.73 m^2 as determined by the 4-variable Modification of Diet in Renal Disease (MDRD) equation, confirmed via a single repeat if deemed necessary.

22. Subjects with a hemoglobin <10 g/dL (100 g/L). Confirmed via a single repeat if deemed necessary.

23. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 X the upper limit of normal (ULN) at the Screening visit (V1), or a total bilirubin >1.5 X the ULN unless the subject has a history of Gilbert's.

24. Subject 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.

25. Subject is on or likely to require treatment for ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids. These medications are not to be used from the time of the start of the Day 1 Visit (Visit 2) to the completion of the trial.

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

26. The following therapeutic agents are prohibited for the duration of the trial. These medications are not to be used from 8 weeks before the Screening visit (V1) until the completion of the trial.

    - Treatment with another SGLT2 inhibitor;
    - Treatment with rosiglitazone;
    - Treatment with chlorpropamide.

27. Subjects who have donated blood or blood products within six weeks of Screening (V1) or who plan to donate blood or blood products at any time during the trial.

28. Subjects who have undergone a surgical procedure within 4 weeks prior to signing informed consent or have planned major surgery during the trial. Note: A subject who has undergone minor surgery within the 4 weeks prior to Screening Visit (V1) 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. For exclusion regarding cardiovascular surgery, see exclusion criterion #3.

29. Subjects with:

    - Known history of Human Immunodeficiency Virus (HIV);
    - Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells.

30. At randomization, subject 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 criterion or which, in the opinion of the investigator, exposes the subject to risk by enrolling in the trial.

31. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality at the Screening visit (V1) that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial.

32. Subjects who have previously been randomized in a trial with ertugliflozin.

33. Participation in other studies involving investigational drug (s) (Phases 1-4) within 30 days before the Screening visit (V1) and/or during trial participation.

34. Subject is pregnant or breast-feeding, or is expecting to conceive during the trial, including 14 days following the last dose of blinded investigational product.

35. Subject is expecting to undergo hormonal therapy in preparation to donate eggs during the period of the trial, including 14 days following the last dose of blinded investigational product.

36. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer/Merck employees directly involved in the conduct of the trial.

4.2.1. Exclusion Criteria – Specific to Insulin with or without Metformin Add-on Glycemic Sub-Study

In addition to above mentioned exclusion criteria for the main cardiovascular study, subjects will not be eligible to be enrolled in this sub-study if they meet any of the following additional exclusion criteria at the time of the Screening visit (V1):

37. Subjects using prandial insulin alone without basal insulin.

4.3. Randomization Criteria

Subjects will be assigned a unique identifier via IVRS at the Screening visit (V1), which will be retained throughout the duration of participation in the trial. Subjects will be randomized into the trial at Day 1 visit (V2), provided that they have satisfied all subject eligibility criteria. Eligibility criteria are outlined in Section 4.1, Section 4.1.1 and Section 4.1.2, and should be verified at the Screening visit (V1) and at the Day 1 visit (V2). A computer-generated randomization code using the method of random permuted blocks will be utilized to assign subjects to 1 of 3 treatment regimens (5 mg ertugliflozin once daily, 15 mg ertugliflozin once daily or matching placebo) on Day 1 visit (V2). For subjects enrolled under the original protocol, the randomization will be stratified by sub-study and by geographic region (within sub-study). The stratification factor for sub-study will have four levels: subjects entering the insulin with or without metformin sub-study on a background of

insulin alone, subjects entering the insulin with or without metformin sub-study on a background of insulin plus metformin, subjects entering the SU monotherapy sub-study and subjects entering the main cardiovascular study but not any of the aforementioned sub-studies. For subjects enrolled under Amendment 1, the randomization will be stratified by geographic region only.

4.4. Life Style Guidelines

4.4.1. Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least **10 hours** prior to any blood sample collection for clinical laboratory tests and fasting glucose testing.

- Subjects who do not fast before a scheduled clinic visit will be required to return fasting for a clinic visit within 7 days.

- On scheduled outpatient visits to the site, subjects must be instructed to arrive **without** having taken the dose of investigational product or any other AHA (if applicable). Other medications may be administered prior to the clinic visit if they can be administered without food. On clinic visit days, subjects may eat to break their fast after the collection of weight, completion of laboratory procedures and blood pressure and pulse rate per the Schedule of Activities. Other AHA therapy should be administered after the subject has consumed a meal, if applicable.

- Subjects will be counseled on appropriate dietary and lifestyle guidelines for T2DM at Day 1 visit (V2) and asked to follow the advice throughout participation in the trial. Counseling on dietary guidelines should be in accordance with local medical standards of care for subjects with T2DM, further details in Section 6.1.2.

4.4.2. Physical Activity

Subjects must not engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, or aerobics) within 48 hours before each blood sample collection for clinical laboratory tests for the duration of their participation in the trial.

4.4.3. Alcohol, Caffeine and Tobacco

- Intake of alcohol should be limited (refer to Exclusion 12 for acceptable amount of alcohol consumption).

- Ingestion of caffeine will be prohibited for at least 30 minutes prior to scheduled electrocardiogram and blood pressure determinations.

- Ingestion of nicotine-containing products will be prohibited for at least 30 minutes prior to scheduled electrocardiogram and blood pressure determinations.

4.4.4. Contraception

Only female subjects of non-childbearing potential as per Section 4.4.4.1, and females of childbearing potential who agree to use adequate methods of contraception, as outlined below in Section 4.4.4.2, will be allowed to enroll in this trial.

4.4.4.1. Females – Non-childbearing Potential

To be considered as non-childbearing potential, female subjects must meet at least one of the following criteria:

1. 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 the Screening visit (V1).

4.4.4.2. Females of Childbearing Potential

Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as (1) surgically sterilized, (2) postmenopausal, (3) not heterosexually active for the duration of this trial (this form of birth control must be accepted by local regulatory agencies and review committees as the sole method of birth control), or (4) heterosexually active and agrees to use (or their partner use) two acceptable methods of contraception to prevent pregnancy within the projected duration of the trial and for 14 days after the last dose of investigational product.

Subjects need to affirm that they meet the criteria for correct use of at least 2 of the selected methods of contraception. The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

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 contraceptive sponge and a 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).

4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the trial contact list provided to each site.

To facilitate access to appropriately qualified medical personnel on trial related medical questions or problems, subjects are provided with a contact card after signing the ICD. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the trial. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however it should only be used in the event that the established communication pathways between the investigational site and the trial team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the trial. The contact number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Approximately 8000 subjects will be randomized in a 1:1:1 ratio to receive 5 mg ertugliflozin once daily, ertugliflozin 15 mg once daily or matching placebo.

Allocation of subjects to treatment groups will proceed through the use of a randomization system (IVRS or equivalent) that is accessible 24 hours per day, 365 days per year. The dispenser will be required to enter or select the information specified by the IVRS user manual. Subject information will be entered into the system starting at the Screening visit (V1) when the subject will be assigned to a unique identifier which will be retained throughout the duration of participation in the trial. On the Day 1 visit (V2), once the inclusion, exclusion and randomization criteria have been verified, each subject will be provided with a subject randomization number. Once subject numbers and randomization numbers have been assigned, they cannot be reassigned.

The investigator must maintain a log linking the subject screening number and randomization number (if applicable) to the subject’s name. The investigator must follow all applicable privacy laws in order to protect a subject’s privacy and confidentiality. Information that could identify a subject will be masked on material received by the sponsor.

5.2. Breaking the Blind

The trial will be subject-, investigator- and sponsor- blinded.

At the initiation of the trial, the sites will be instructed on the method for breaking the blind. The method will be an electronic process via IVRS. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should consult with a member of the sponsor trial team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered in the source documents.

5.3. Drug Supplies

5.3.1. Formulation and Packaging

Ertugliflozin 5 mg, ertugliflozin 10 mg and matching placebos will be supplied as immediate release tablets for oral administration. Tablets will be packaged into bottles.

Pfizer will provide investigator sites with sufficient amounts of blinded investigational product to accommodate expected recruitment. Investigational product will be assigned to subjects via IVRS or equivalent.

All investigational product containers dispensed to subjects should be returned to the investigator site at the next clinic visit for assessment of subject compliance and drug accountability.

5.3.2. Administration

On Day 1, each subject will be randomly assigned to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo.

The trial utilizes a double-dummy approach to maintain double-blinding, with a placebo tablet matching the ertugliflozin 5 mg tablet and another placebo tablet matching the ertugliflozin 10 mg tablet. Subjects randomized to ertugliflozin 5 mg will be instructed to take 1 ertugliflozin 5 mg tablet and 1 placebo tablet matching the ertugliflozin 10 mg tablet per day. Subjects randomized to ertugliflozin 15 mg will be instructed to take 1 ertugliflozin 5 mg tablet and 1 ertugliflozin 10 mg tablet per day. Subjects randomized to placebo will take 1 placebo tablet matching the ertugliflozin 5 mg tablet and 1 placebo tablet matching the ertugliflozin 10 mg tablet per day. Thus, all subjects will take two tablets each day of ertugliflozin/placebo.

The investigational product should be taken orally in the morning at approximately the same time of day from Day 1 visit (V2) through to the end of the trial or early termination. In addition, subjects will be instructed to delay the self-administration of investigational product and other AHA(s), if applicable, on the days of their visits, when the visit assessments should be completed prior to administration.

If a subject misses a dose of investigational product during the trial, they should be instructed to take it as soon as they remember unless it is time for the next dose. Subjects should be instructed not to “make-up” for the missed dose by taking a double dose at the same time or on the same day.

5.3.3. Compliance

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 investigational product.

Compliance for subjects must be assessed for the investigational product by taking the subject's report.

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

5.4. Drug Storage and Drug Accountability

The blinded investigational product dispensing and accountability will be managed by IVRS and monitored by clinical research associates (CRAs) in addition to the investigational product inventory monitoring at each site. The investigator, or an approved representative, eg, pharmacist, will ensure that all medication is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements.

Storage conditions stated in the SRSD [Investigator Brochure's (IB)] will be superseded by the conditions stated on the investigational product label.

The investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product(s). Pfizer or its designee may supply drug accountability forms that must be used or may approve use of standard institution forms.

At the end of the trial, Pfizer or its designee will provide instructions as to disposition of any unused investigational product. If Pfizer or its designee authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer or its designee. Destruction must be adequately documented.

5.5. Concomitant Medication(s)

All AHA(s) received by the subject at any time prior to the Screening visit (V1) and non-AHA(s) taken within **8 weeks before the Screening visit (V1),** during the interval between the Screening period and randomization and those taken throughout the trial will be recorded on the appropriate electronic case report form (eCRF). The site may rely on subject report for this information. All subjects must be questioned about concomitant medication at each visit.

Medications that are indicated as prohibited in the Exclusion Criteria must not be used within 8 weeks before the Screening visit (V1) during the interval between the Screening period and randomization or during the trial as specified in Section 4.2.

5.5.1. Treatment for Glycemic Control for Type 2 Diabetes

To enable an assessment of the glycemic effects of ertugliflozin (or dietary and exercise counseling alone for subjects randomized to placebo), doses of background AHA medications will be required to be held constant in **all** subjects enrolled in this trial for the initial 18 weeks of the trial **with two exceptions**:

First, subjects will be prescribed glycemic rescue therapy if they meet specific, progressively more stringent, glycemic thresholds (see Table 3) based on a **repeated, confirmed** FPG measured by the **central lab** according to the directions below. Subjects who require a repeat FPG to determine if they meet the criterion for glycemic rescue therapy should have the repeat FPG measurement performed as early as possible (within approximately 7 days following the receipt of initial test results).

Second, a subject experiencing clinically significant hypoglycemia according to the investigator at any time during the trial is permitted to have the dose of appropriate background AHA (eg, insulin, SU, glinide) reduced or discontinued as per the judgment of the investigator or the treating physician.

Choice and dosing of glycemic rescue will be at the discretion of the investigator or the treating physician and they will be responsible for managing the initiation and titration of the glycemic rescue therapy consistent with standards of care for management of patients with T2DM within the country of the investigational site. If glycemic rescue therapy is initiated by the investigator it can be initiated at a scheduled or unscheduled visit but not during a telephone call. For details on the Glycemic Rescue Visit see Section 6.5.

Following the Week 18 visit (V5), the investigator/treating physician is able to make any changes in the subject's AHA treatment regimen to achieve an appropriate HbA1c level for the subject (with exception of prohibited concomitant medications listed in Section 4.2).

Details on the specific glycemic rescue criteria for the initial 18 weeks of the trial are provided in Table 3 below.

Table 3. Glycemic Rescue Criteria for All Subjects for the First 18 Weeks

Randomization through Week 6	FPG >270 mg/dL (15.0 mmol/L)
After Week 6 through Week 12	FPG >240 mg/dL (13.3 mmol/L)
After Week 12 through Week 18	FPG >200 mg/dL (11.1 mmol/L)

Subjects who receive glycemic rescue therapy will continue taking investigational product for the duration of the trial unless they meet withdrawal criteria as per Section 6.7.4.

5.5.2. Treatment for Secondary Prevention of Cardiovascular Disease

Subjects may be administered other medications necessary for the treatment of concomitant medical disorders, particularly other disorders that are cardiovascular risk factors, including but not limited to hypertension and dyslipidemia. Attention should be placed on appropriate use of medications recommended in local country or national guidelines including anti-platelet therapy, statins and angiotensin-converting enzyme (ACE) inhibitors. Smokers should be counseled to quit and receive treatment if needed.

Subjects enrolled in this trial should continue to be treated by their treating physician who normally manages their cardiovascular disease and prescribes medication for the subject´s cardiovascular disease. The investigator or the treating physician is able to make any changes in the subject's background cardiovascular treatment regimen to achieve appropriate targets for secondary disease prevention at any time during the trial.

All concomitant medication administration will be recorded on the eCRF.

6. STUDY PROCEDURES

The same visit schedule will be followed by all subjects, those in the main cardiovascular study and those in the sub-studies.

Centers should attempt to schedule each subject's visits at approximately the same time of day for that subject.

Recommended visit windows are detailed for each visit in the corresponding sections.

For the procedures described below, where multiple procedures are scheduled at the same visit, the following chronology of events should be adhered to, where possible:

- *12-lead ECG:* obtain prior to vital signs assessment, blood samples, and prior to dosing.
- *Vital Signs (blood pressure and pulse rate):* obtain after 12-lead ECG collection but prior to obtaining blood samples and prior to dosing.
- *Fasting blood and urine samples:* prior to dosing but after assessment of 12-lead ECG, and vital signs.
- *Other procedures:* all other procedures may be obtained before or after blood specimen collection.

6.1. Instructions to Subjects

At the Day 1 visit (V2), subjects will be given the following instructions/guidance to be complied with for the duration of their participation in the trial and provided the following or similar items to aid in the management of their T2DM (provided to the sites by the sponsor):

- Home glucose monitoring supplies including a sponsor-provided glucose meter and accompanying supplies;

- Hypoglycemia Assessment Log and Self –Monitoring Blood Glucose log to be completed at home and brought to **each** outpatient visit to the site along with the glucose meter;

- Instructions for home glucose monitoring:

  - Recommended frequency for routine home glucose monitoring will be determined for each subject by the investigator.

  - Home glucose monitoring should also be undertaken in the event that subjects experience symptoms of hyperglycemia or hypoglycemia.

6.1.1. Dispense Hypoglycemia Assessment Log and Instruct on Hypoglycemia Symptoms and Management

At Day 1 visit (V2), the site will review the symptoms and management of hypoglycemia with the subject. The site will counsel the subject to perform a fingerstick glucose measurement if any symptoms occur that may be related to hypoglycemia (eg, 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 for any symptomatic episode he or she believes may represent hypoglycemia. If a fingerstick glucose has been obtained before or shortly (ie, within a few minutes) after treatment, 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 clinical symptoms.

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

- Any episode of hypoglycemia for which assistance was required (ie, 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 in the log. Each episode should be evaluated by the investigator and recorded on the Hypoglycemia Assessment (HA) eCRF. For episodes determined to be hypoglycemia (symptomatic or asymptomatic), and for all glucose values ≤70 mg/dL (3.9 mmol/L), regardless of whether they are considered an adverse event, the HA eCRF must also be completed. Each event of symptomatic hypoglycemia must be reported as an adverse event on the adverse event eCRF. Each episode of asymptomatic

hypoglycemia considered by the investigator to be an adverse event should also be reported on the adverse event eCRF.

6.1.2. Diet and Exercise Counseling

Subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at Day 1 visit (V2) only; monitoring at other visits may be done by other appropriate site personnel evaluating the subject.

At Day 1 visit (V2), the subject will receive counseling on diet consistent with local guidelines. At each subsequent visit, the subject will be asked about their diet and exercise. Detailed dietary information will not be captured.

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

6.2. Screening

6.2.1. Screening (Visit 1)

As subjects must be fasting for the Screening visit (V1), it is permissible that the ICD is signed by the subject prior to the Screening visit (V1). Because some of the laboratory data at the Screening visit (V1) can be repeated (see Exclusion Criteria Section 4.2), the Screening visit (V1) may actually occur over several days.

Subjects will be instructed to arrive at the site after a minimum **10-hour fast** (except water) in order to have the blood tests done at the Screening visit (V1). At this visit, the following procedures will be completed to confirm that they meet the eligibility criteria for this trial:

- Obtain informed consent if not obtained previously (Section 12.3). 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.
- Contact IVRS.
- Collect demography, medical history including cardiac ejection fraction (if available) for all subjects, smoking status, as well as concomitant medications used.
- Measure body weight and height in duplicate (Section 7.4).
- Obtain 12-lead ECG (Section 7.5).
- Obtain sitting triplicate blood pressure and pulse rate measurements (Section 7.7).
- Perform an optional fingerstick HbA1c assessment while at the site. The fingerstick HbA1c cannot substitute for a central laboratory measurement to determine subject eligibility.
- Obtain blood **and** urine specimens for:

- Chemistry (Section 7.9);
- Hematology (Section 7.9);
- Urinalysis (Section 7.9);
- Fasting triglycerides and TSH (Section 7.9);
- HbA1c and FPG (Section 7.9);
- Urine pregnancy test for women of child-bearing potential (Section 7.1.6).

- Assess eligibility: Adequate documentation of objective evidence that the subject has established vascular disease must be available prior to Day 1 visit (V2) through the investigational site's medical records, copies of such records from other institutions, or a letter from a referring physician that specifically states the diagnosis and date of the most recent occurrence of the qualifying event(s) or procedure(s).

6.3. Double-Blind Treatment Period

6.3.1. Visits During Year 1

6.3.1.1. Day 1 (Visit 2) – Randomization Visit

Subjects who meet the trial eligibility based on assessments performed at the Screening visit (V1) will return to the clinic at Day 1 visit (V2) for randomization into the trial. The randomization visit, Day 1 visit (V2) is to take place approximately 1 to 4 weeks following the Screening visit (V1)**.** Background AHA treatment must continue to remain stable throughout the length of the Screening period.

Subjects will return to the site after a minimum **10-hour fast** (except water) for the Day 1 visit (V2). At this visit, the following procedures will be completed:

- Review and confirm eligibility criteria.
- Update concomitant medications since last visit.
- Measure body weight in duplicate (Section 7.4).
- Complete physical examination (Section 7.3).
- Obtain duplicate orthostatic blood pressure and pulse rate measurement (supine → standing) (Section 7.8).
- Obtain triplicate sitting blood pressure and pulse rate measurements (Section 7.7).
- Obtain blood **and** urine specimens for:

- Chemistry (Section 7.9);
- Hematology (Section 7.9);
- Urinalysis (Section 7.9);
- HbA1c and FPG (Section 7.9);
- Urinary albumin/creatinine ratio (Section 7.9.2);
- Lipid panel (Section 7.9.1);
- Urine pregnancy test for women of child-bearing potential (Section 7.1.6);
- Whole blood (DNA), plasma and serum for Future Biomedical Research (FBR) (Appendix 1). The FBR sample for DNA analysis should be obtained pre dose, at the Day 1 visit (V2) as the last sample drawn, on subjects who qualify for randomization, but may be obtained at a later date during the trial after the FBR informed consent is obtained.

- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Assessment of potential cardiovascular event(s) (Section 7.1).
- Subjects will be instructed on exercise and dietary guidelines for management of T2DM consistent with local standards of care by a dietician or qualified healthcare professional Section 6.1.2.
- Subjects will be given a sponsor-provided glucose meter, a self-monitoring blood glucose log and needed supplies to enable them to perform fingerstick blood glucose self- monitoring at home. Subjects should be instructed on how to complete the log (Section 6.1).
- As a means of confirming subject´s understanding of the instructions, subject will perform a fasting fingerstick blood glucose assessment while at the site.
- Subjects will be educated on the symptoms of hyperglycemia (ie, polyuria, polydipsia) and instructed to call the site should these symptoms occur and/or worsen before next visit.
- Subjects will be given a hypoglycemia assessment log that they must use to track episodes of hypoglycemia. Subjects should be educated on the symptoms and management of hypoglycemia (Section 6.1.1).
- Subjects will be instructed to contact the site if they are admitted to hospital for any reason or if they experience a cardiovascular event.

- Register/randomize the subjects into trial using IVRS (Section 4.3 and Section 5.1).
- Provide subjects with study contact card (Section 4.5).
- Subjects will be administered the first witnessed dose of investigational product before leaving the site.
- Subjects will be provided with investigational product to last until the next visit.

6.3.1.2. Week 6 (Visit 3)

At Week 6 ± 7 days relative to Day 1 visit (V2), subjects will return to the site after a minimum **10-hour fast** (except water). At this visit, the following procedures will be completed:

- Contact IVRS.
- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Update concomitant medications since last visit.
- Measure body weight in duplicate (Section 7.4).
- Obtain duplicate orthostatic blood pressure and pulse rate measurement (supine → standing) (Section 7.8).
- Obtain triplicate sitting blood pressure and pulse rate measurements (Section 7.7).
- Obtain blood **and** urine specimens for:
  - Chemistry (Section 7.9);
  - Hematology(Section 7.9);
  - HbA1c and FPG (Section 7.9);
  - Urine pregnancy test for women of child-bearing potential (Section 7.1.6);
- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Assessment of potential cardiovascular event(s) (Section 7.1);
- Review hypoglycemia assessment and self-monitoring blood glucose logs completed by the subjects (Section 7.6);

- Diet and exercise monitoring (Section 6.1.2);
- Subjects will be instructed to contact the site if they are admitted to hospital for any reason or if they experience a cardiovascular event.

Following completion of the above procedures:

- Provide subjects with glucose meter supplies and additional self-monitoring blood glucose and hypoglycemia assessments logs as needed;
- Subjects will be provided investigational product to last until the next visit.

6.3.1.3. Week 12 (Visit 4)

At Week 12 ± 7 days relative to Day 1 visit (V2), subjects will return to the site after a minimum **10-hour fast** (except water). At this visit, the following procedures will be completed:

- Contact IVRS.
- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Update concomitant medications since last visit.
- Measure body weight in duplicate (Section 7.4).
- Obtain sitting triplicate blood pressure and pulse rate measurements (Section 7.7).
- Obtain blood **and** urine specimens for:
  - Chemistry (Section 7.9);
  - HbA1c and FPG (Section 7.9);
  - Urine pregnancy test for women of child-bearing potential (Section 7.1.6).
- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Assessment of potential cardiovascular event(s) (Section 7.1).
- Review hypoglycemia assessment and self-monitoring blood glucose logs completed by the subjects (Section 7.6).
- Diet and exercise monitoring (Section 6.1.2).

- Subjects will be instructed to contact the site if they are admitted to hospital for any reason or if they experience a cardiovascular event.

Following completion of the above procedures:

- Provide subjects with glucose meter supplies and additional self-monitoring blood glucose and hypoglycemia assessments logs as needed.
- Subjects will be provided with investigational product to last until the next visit.

6.3.1.4. Week 18 (Visit 5)

At Week 18 ± 7 days relative to Day 1 visit (V2), subjects will return to the site after a minimum **10-hour fast** (except water). At this visit, the following procedures will be completed:

- Contact IVRS.
- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Update concomitant medications since last visit.
- Measure body weight in duplicate (Section 7.4).
- Obtain 12-lead ECG (Section 7.5).
- Obtain sitting triplicate blood pressure and pulse rate measurements (Section 7.7).
- Obtain blood **and** urine specimens for:
  - Chemistry (Section 7.9);
  - Hematology(Section 7.9);
  - Urinalysis(Section 7.9);
  - HbA1c and FPG (Section 7.9);
  - Urinary albumin/creatinine ratio (Section 7.9.2);
  - Lipid panel (Section 7.9.1);
  - Urine pregnancy test for women of child-bearing potential (Section 7.1.6);
  - Plasma and serum for Future Biomedical Research.

- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Assessment of potential cardiovascular event(s) (Section 7.1).
- Review hypoglycemia assessment and self-monitoring blood glucose logs completed by the subjects (Section 7.6).
- Diet and exercise monitoring (Section 6.1.2).
- Subjects will be instructed to contact the site if they are admitted to hospital for any reason or if they experience a cardiovascular event.

Following completion of the above procedures:

- Provide subjects with glucose meter supplies and additional self-monitoring blood glucose and hypoglycemia assessments logs as needed.
- Subjects will be provided with investigational product to last until the next visit.

6.3.1.5. Week 26 (Visit 6)

At Week 26 ± 7 days relative to Day 1 visit (V2), subjects will return to the site after a minimum **10-hour fast** (except water). At this visit, the following procedures will be completed:

- Contact IVRS.
- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Update concomitant medications since last visit.
- Measure body weight in duplicate (Section 7.4).
- Obtain duplicate orthostatic blood pressure and pulse rate measurement (supine → standing) (Section 7.8).
- Obtain sitting triplicate blood pressure and pulse rate measurements (Section 7.7).
- Obtain blood **and** urine specimens for:
  - Chemistry (Section 7.9);
  - Hematology (Section 7.9);
  - Urinalysis (Section 7.9);

- HbA1c and FPG (Section 7.9);
- Urine pregnancy test for women of child-bearing potential (Section 7.1.6).

- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Assessment of potential cardiovascular event(s) (Section 7.1).
- Review hypoglycemia assessment and self-monitoring blood glucose logs completed by the subjects (Section 7.6).
- Diet and exercise monitoring (Section 6.1.2).
- Subjects will be instructed to contact the site if they are admitted to hospital for any reason or if they experience a cardiovascular event.

Following completion of the above procedures:

- Provide subjects with glucose meter supplies and additional self-monitoring blood glucose and hypoglycemia assessments logs as needed.
- Subjects will be provided with investigational product to last until the next visit.

6.3.1.6. Week 39 (Visit 7)

At Week 39 ± 14 days relative to Day 1 visit (V2), subjects will return to the site after a minimum **10-hour fast** (except water). At this visit, the following procedures will be completed:

- Contact IVRS.
- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Update concomitant medications since last visit.
- Measure body weight in duplicate (Section 7.4).
- Obtain sitting triplicate blood pressure and pulse rate measurements (Section 7.7).
- Obtain blood **and** urine specimens for:
  - Chemistry (Section 7.9),
  - HbA1c and FPG (Section 7.9),

- Urine pregnancy test for women of child-bearing potential (Section 7.1.6).

- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "How do you feel?"

- Assessment of potential cardiovascular event(s) (Section 7.1).

- Review hypoglycemia assessment and self-monitoring blood glucose logs completed by the subjects (Section 7.6).

- Diet and exercise monitoring (Section 6.1.2).

- Subjects will be instructed to contact the site if they are admitted to hospital for any reason or if they experience a cardiovascular event.

Following completion of the above procedures:

- Provide subjects with glucose meter supplies and additional self-monitoring blood glucose and hypoglycemia assessments logs as needed.

- Subjects will be provided with investigational product to last until the next visit.

6.3.1.7. Week 52 (Visit 8)

At Week 52 ± 14 days relative to Day 1 visit (V2), subjects will return to the site after a minimum **10-hour fast** (except water). At this visit, the following procedures will be completed:

- Contact IVRS.

- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.

- Update concomitant medications since last visit.

- Measure body weight in duplicate (Section 7.4).

- Brief physical examination (Section 7.3).

- Obtain 12-lead ECG (Section 7.5).

- Obtain sitting triplicate blood pressure and pulse rate measurements (Section 7.7).

- Obtain blood **and** urine specimens for:

  - Chemistry (Section 7.9);

- Hematology (Section 7.9);
- Urinalysis (Section 7.9);
- HbA1c and FPG (Section 7.9);
- Urinary albumin/creatinine ratio (Section 7.9.2);
- Lipid panel (Section 7.9.1);
- Urine pregnancy test for women of child-bearing potential (Section 7.1.6);
- Plasma and serum for Future Biomedical Research.

- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Assessment of potential cardiovascular event(s) (Section 7.1).
- Review hypoglycemia assessment and self-monitoring blood glucose logs completed by the subjects (Section 7.6).
- Diet and exercise monitoring (Section 6.1.2).
- Subjects will be instructed to contact the site if they are admitted to hospital for any reason or if they experience a cardiovascular event.

Following completion of the above procedures:

- Provide subjects with glucose meter supplies and additional self-monitoring blood glucose and hypoglycemia assessments logs as needed.
- Subjects will be provided with investigational product to last until the next visit.

6.3.2. Visits Following Year 1

Following the first year of double-blind treatment, subjects will return for clinic visits after a minimum **10-hour fast** (except water) on an every 4 month ± 1 month period (ie, Months 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56 and 60) until completion of the trial; where completion is the occurrence of the required number of adjudicated primary cardiovascular endpoints.

The procedures to be completed at these visits are as follows:

- Contact IVRS – **All visits**.
- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed. – **All visits**.

- Update concomitant medications since last visit – **All visits**.
- Measure body weight in duplicate (Section 7.4) – **All visits**.
- Brief physical examination (Section 7.3) – **Months 24, 36, 48, 60.**
- 12-Lead ECG (Section 7.5) – **Months 24, 36, 48, 60.**
- Obtain sitting triplicate blood pressure and pulse rate measurements (Section 7.7) – **All visits.**
- Obtain blood **and** urine specimens for:
  - HbA1c and FPG (Section 7.9) – **All visits**.
  - Chemistry (Section 7.9) – **All Visits.**
  - Hematology (Section 7.9) – **Months 24, 36, 48, 60.**
  - Urinalysis (Section 7.9) – **Months 24, 36, 48, 60.**
  - Urinary albumin/creatinine ratio (Section 7.9.2) – **Months 24, 36, 48, 60.**
  - Lipid panel (Section 7.9.1) – **Months 24, 36, 48, 60**.
  - Urine pregnancy test for women of child-bearing potential (Section 7.1.6) – **All visits.**
- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "how do you feel?" – **All visits.**
- Assessment of potential cardiovascular event(s) (Section 7.1) – **All visits.**
- Review hypoglycemia assessment and self-monitoring blood glucose logs completed by the subjects (Section 7.6) – **All visits.**
- Diet and exercise monitoring (Section 6.1.2). – **All visits.**
- Subjects will be instructed to contact the site if they are admitted to hospital for any reason or if they experience a cardiovascular event – **All visits.**
- Provide subjects with glucose meter supplies and additional self-monitoring blood glucose and hypoglycemia assessments logs as needed. – **All visits, (except End of Study or Early Termination visits).**
- Subjects will be provided with investigational product to last until the next visit – **All visits (except End of Study or Early Termination visits).**

If the trial is not complete by Visit 20 (Month 60), visits will continue on an every 4 month ± 1 month schedule and the list of procedures to be performed are the same as for the visits for Months 52, 56 and 60 respectively. For example, assessments at Month 64 are identical to Month 52, assessments at Month 68 are identical to Month 56 and assessments at Month 72 are identical to Month 60.

6.3.3. End of Study Visit/Early Termination Visit

The trial sponsor will provide the best estimate of when the pre-specified required number of adjudicated primary cardiovascular endpoints has occurred in the trial. After the sponsor recommendation to close the trial, all investigators will receive communication with a recommendation to contact trial subjects for completion of an End of Study Visit. Subjects who complete the trial on investigational product or those who discontinue investigational product prematurely, should complete the procedures listed below even if they are not taking investigational product when the trial is terminated.

The following procedures will occur at this visit after a minimum **10-hour fast** (except water):

- Contact IVRS.
- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Update concomitant medications since last visit.
- Measure body weight in duplicate (Section 7.4).
- Brief physical examination (Section 7.3).
- 12-Lead ECG (Section 7.5)**.**
- Obtain sitting triplicate blood pressure and pulse rate measurements (Section 7.7)**.**
- Obtain blood **and** urine specimens for:
  - Chemistry (Section 7.9);
  - Hematology (Section 7.9);
  - Urinalysis (Section 7.9);
  - HbA1c and FPG (Section 7.9);
  - Urinary albumin/creatinine ratio (Section 7.9.2);
  - Lipid panel (Section 7.9.1);

- Urine pregnancy test (women of childbearing potential) (Section 7.1.6);
- Plasma and serum for Future Biomedical Research.

- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "how do you feel?"
- Assessment of potential cardiovascular event(s) (Section 7.1).
- Review hypoglycemia assessment and self-monitoring blood glucose logs completed by the subjects (Section 7.6).
- Diet and exercise monitoring (Section 6.1.2).

6.4. Follow-up Phone Call

Each randomized subject should have a follow-up phone call 14 days after the last dose of investigational product to assess for AEs, SAEs and collect information on clinical events (Section 7.1), if applicable. The phone call should be completed within a ± 3 day window.

6.5. Glycemic Rescue Visit (if Applicable)

Subjects who require glycemic rescue therapy during the first 18 weeks of the trial as per Section 5.5.1 will have glycemic rescue therapy initiated at either a scheduled or unscheduled visit. Glycemic rescue therapy can also be initiated by a non-study physician. If glycemic rescue therapy is initiated by a non-study physician, subjects should be instructed to inform the site. In that case, subjects should be requested to attend the site at an unscheduled visit for the relevant laboratory tests/assessments as indicated below. The following procedures are to be completed at a Glycemic Rescue Visit:

- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Update concomitant medications since last visit.
- Measure body weight in duplicate (Section 7.4).
- Obtain duplicate orthostatic blood pressure and pulse rate measurement (supine → standing) (Section 7.8).
- Obtain sitting triplicate blood pressure and pulse rate measurements (Section 7.7).
- Brief physical examination (Section 7.3).
- Obtain blood **and** urine specimens for:
  - Chemistry (Section 7.9),

- Hematology (Section 7.9),
- Urinalysis (Section 7.9),
- HbA1c (only if visit is at least 6 weeks after randomization) and FPG (Section 7.9),
- Lipid panel (Section 7.9.1),
- Urine pregnancy test (women of childbearing potential) (Section 7.1.6),
- Plasma and serum for Future Biomedical Research.

- Conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Assessment of potential cardiovascular event(s) (Section 7.1.1).
- Review hypoglycemia assessment and self-monitoring blood glucose logs completed by the subjects (Section 7.6).
- Diet and exercise monitoring (Section 6.1).

6.6. Discontinuation of Investigational Product

All efforts should be made to follow randomized subjects for the entire duration of the study. Discontinuation of investigational product does not imply or constitute withdrawal of the subject from the study.

Subjects who temporarily or permanently discontinue treatment with investigational product, should remain in the study and continue to be followed for collection of information on cardiovascular events, other events eligible for adjudication, and SAEs. Investigators should try to obtain the most complete collection of data as possible, weighing the subject's willingness to participate with the scientific integrity of the protocol. The protocol offers subjects the option of continuing in the study off investigational product by: (1) attending the normally scheduled clinic visits; (2) attending the annual clinic visits only; (3) receiving phone contacts to collect information on cardiovascular events/SAEs, without attending clinical visits. The site phone contacts could occur either at the time of the normally scheduled visits or they could occur just annually and/or at the completion of the trial. The sole exception to this requirement is when a subject fully withdraws consent for both continued treatment with investigational product and study procedures (see Section 6.7).

Subjects who have not withdrawn consent, but who have discontinued from investigational product may initiate any other therapy as needed (previously prohibited medications may be used). Permanent discontinuation of investigational product must be registered in IVRS.

As noted above, if a subject has not fully withdrawn consent for further contact with the study site, the subject should be encouraged to remain in contact with the investigator, either by attending study visits or via phone contacts, throughout the remainder of the study. The study sponsor team will provide to the study site, information regarding a "clinicians' hotline", to be used by investigators to contact a member of the study team after a subject discontinues investigational product. The objective of this call is to ensure that investigators (and by extension subjects) are aware of the importance of continued follow-up in the study after investigational product discontinuation and of the multiple options available for continued study participation. Every effort must be made to retain subjects in the study, even if they are no longer taking investigational product as it is important to the scientific integrity of the protocol.

6.7. Subject Withdrawal

6.7.1. Withdrawal of Consent

Subjects who request to discontinue investigational product will remain in the study and must continue to be followed as outlined in Section 6.6. The only exceptions to this are when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information, or when a subject dies. Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal represents the discontinuation from further treatment with investigational product only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. As vital status (whether the subject is alive or dead) is being measured in this study, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site. 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 are reasons for withdrawal of consent. In such circumstances, subjects should be encouraged to remain in contact with the investigator, either by attending study visits or via phone contacts throughout the remainder of the study as described in Section 6.6 in order to provide safety information as it occurs.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. When a subject has missed a scheduled visit, every attempt should be made to contact him/her, to reschedule the visit, by phone, e mail, text message, and if necessary, by letter and/or certified mail, in instances where the subject is not responsive to contact attempts. The study team must be contacted, ideally through the "clinicians' hotline", to discuss strategies available for assistance with locating subjects who are potentially lost to follow-up. All efforts to retain a subject should continue throughout the course of the study

and should be documented in the subject's medical source record. No subject should be considered lost to follow-up, until the study has been completed. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for study drug discontinuation, request that the subject return all unused investigational product, request that the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

Every effort should be made to ensure that all subjects complete study participation. Subjects who discontinue study treatment will be asked and encouraged to continue participation in the study as described above.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, 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 such withdrawal of consent.

6.7.2. Avoiding Lost to Follow-Up

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. When a subject has missed a scheduled visit, every attempt should be made to contact him/her, to reschedule the visit, by phone, e mail, text message, and if necessary, by letter and/or certified mail, in instances where the subject is not responsive to contact attempts. The study team must be contacted, ideally through the "clinicians' hotline", to discuss strategies available for assistance with locating subjects who are potentially lost to follow up. All efforts to retain a subject should continue throughout the course of the study and should be documented in the subject's medical source record. No subject should be considered lost to follow up, until the study has been completed. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for study drug discontinuation, request that the subject return all unused investigational product, request that the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

Lost to follow-up is defined by the inability to reach the subject by the end of the study only. All reasonable efforts must be made to locate subjects who miss scheduled study visits to determine and report their ongoing status. Sites should make at least three attempts for a telephone contact. If the three attempts of telephone contact are unsuccessful, sites should make at least two attempts to reach the subject via certified letter. Procedures will be put in place and described in the Informed Consent Document to ensure that if a subject loses contact with the trial site, alternative measures will be utilized for the follow-up portion of the study including the collection of information on cardiovascular events. This may include contacting family members and health care providers and, when applicable, using subject location services. Continued attempts to contact the subject must be performed, until the study is completed. This includes follow-up with persons authorized by the subject as noted above. All attempts at contacting the subject must be documented in the subject's medical records.

If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

6.7.3. 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 (clinical.specimen.management@merck.com), 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 (eg, if the investigator is no longer required by regulatory agencies to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

6.7.4. Reasons for Discontinuation from Investigational Product or from the Trial

The investigator or sub-investigator is able to interrupt or discontinue investigational product if he/she feels that interruption or discontinuation is necessary for safety or behavioral reasons. The investigational product can also be restarted based on the judgment of the investigator. Notably, occurrence of a non-fatal cardiovascular event or a SAE should not automatically result in interruption or discontinuation of investigational product and the subject should continue to receive investigational product unless interruption or discontinuation is deemed to be clinically necessary.

Reasons for protocol-specified discontinuation from the investigational product or from the trial are listed, but not limited to, below. All subjects will be followed until resolution (ie, return to baseline values or diagnosis determined or new stable state established, based upon investigator and sponsor or its designated representative assessment) for any laboratory safety test abnormality resulting in discontinuation from investigational product.

Withdrawal from the Trial

1. Subject requests withdrawal from the trial.

2. Death.

Discontinuation of Investigational Product

3. Elevation in ALT and/or AST that meet the definition of a potential Case of Drug-Induced Liver Injury per Section 8.7.

4. Parameters of Renal Function: Investigational product is to be discontinued if the eGFR falls to <15 mL/min/1.73m^2 and where the value is confirmed by a second measurement. Additionally, any subject who requires renal replacement therapy will also have investigational product discontinued.

   A confirmed value is defined as a repeat measurement performed within 7 days of notification from the central laboratory of the initial results.

5. Requirement for one of the prohibited medications listed in Section 4.2.

6. Pregnancy.

   Note: A positive urine pregnancy test requires immediate interruption of investigational product until serum human chorionic gonadotropin beta-subunit test (β-hCG) can be performed and found to be negative. Subject must be permanently discontinued and pregnancy should be reported and followed per Section 8.3 if pregnancy is confirmed by a positive serum pregnancy test.

7. The investigator or subject becomes aware of the subject's treatment assignment.

If a subject discontinues investigational product, he/she should complete all Early Termination Visit procedures as described in Section 6.3.3 and listed in Schedule of Activities. Unless the consent to follow the subject is specifically withdrawn, the subject will continue in the trial off investigational product until the end of the trial as outlined in Section 6.6.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The trial team will be informed of these incidents in a timely fashion.

All biological samples will be assayed by a sponsor-identified laboratory, using an analytical method in compliance with standard and validated methodologies, with adherence to written standard operating procedures.

Details regarding the sample processing, handling, storage, and shipment will be offered separately in the study-specific central laboratory manual prior to the initiation of the trial.

7.1. Clinical Event Adjudication

7.1.1. Cardiovascular Events, Venous Thromboembolic Events, and All Deaths

Cardiovascular disease is a major cause of mortality for subjects with T2DM. In order to evaluate the cardiovascular safety of ertugliflozin and to meet regulatory requirements for the assessment of cardiovascular safety of any new diabetic therapy, serious cardiovascular events and all deaths will be adjudicated in this trial (including events from subjects who continue to be followed after discontinuation of investigational product), and across the Phase 2 and 3 ertugliflozin program. The EAC will be comprised of an external panel of independent physicians experienced in assessing cardiovascular endpoints. The panel will be blinded to treatment assignments. The members of the EAC will not be an investigator in any trial for ertugliflozin. 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 Endpoint Adjudication Committee 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 investigational product. The collection period will continue through study completion/end-of-study whether or not the subject continues to receive investigational product unless the subject is unwilling to be contacted by the personnel at the investigational site.

Clinical cardiovascular events occurring between the Screening visit (the time of informed consent) and double-blind treatment randomization will not be adjudicated as that subject will be excluded from the trial as per Section 4.2.

The identification of a potential clinical cardiovascular event will be made by the trial site or by Pfizer or designee. The site will communicate the event to Pfizer or designee within 24 hours of awareness of the potential clinical cardiovascular event using the appropriate CRF module. Pfizer or designee will in turn provide a listing of specific documents needed to support adjudication by the EAC. 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.

7.1.2. Fractures

Spontaneously reported fractures will be adjudicated by an independent and blinded external fracture adjudication committee. In the event that a subject experiences a clinical fracture during the trial, the radiographs and/or local radiologist report and other relevant documentation will be sent to an independent external committee comprised of radiologists. 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 (ie, high-trauma, low-trauma, pathological fracture, stress fracture, and other fracture). The radiologists will not be investigators or sub-investigators in any trial in the Phase 3 program and they will be blinded to the subject's assigned treatment group. A Fracture Adjudication Committee charter will describe the precise mandates and procedures to be used for the adjudication of clinical fractures.

7.1.3. 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 3 program will be adjudicated by an independent external panel of physicians experienced in assessing pancreatic disease. The panel will blinded to treatment assignment. A Pancreatitis Adjudication Charter will describe the precise mandates and procedures to be used for the adjudication of pancreatitis.

7.1.4. 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.

7.1.5. Acute Renal Failure

Ertugliflozin increases urinary glucose excretion leading to an osmotic diuresis, and has the potential to reduce estimated GFR. As part of the overall assessment of renal safety, events reported in this trial and throughout the phase 3 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.

7.1.6. Ketoacidosis

Cases of ketoacidosis (KA) have been reported with marketed SGLT2 inhibitors. Events reported in this trial and throughout the program that meet pre-specified criteria for a potential ketoacidosis event will be adjudicated by an Internal Case Review Committee experienced in diabetes. The committee will be blinded to treatment assignment. A Ketoacidosis Internal Case Review Committee Charter will describe the precise mandates and procedures to be used for the identification and adjudication of events.

7.2. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed at the Screening visit (V1), before investigational product administration at Day 1 visit (V2) and a positive result may be confirmed with a serum pregnancy test. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when a potential pregnancy is otherwise suspected), repeated at visits listed in the Schedule of Activities, and at the end of the trial to confirm the subject has not become pregnant during the trial. In the case of a positive serum hCG test, the subject will be discontinued from investigational product but should continue to be contacted according to the same schedule as if he/she were still taking investigational product, see Section 6.6 for instructions on follow up of subject withdrawal. Pregnancy tests may also be repeated as per request of institutional review boards/ethics committees (IRB/IECs) or if required by local regulations.

7.3. Physical Examinations

A complete physical examination will be performed at the Day 1 visit (V2). A brief physical examination including assessment of the heart, lungs, abdomen, extremities, and skin will be performed at the times listed in the Schedule of Activities. Abnormalities considered clinically significant should be reported as AEs. Other body systems may be evaluated as per judgment of the investigator or as needed to evaluate adverse events.

7.4. 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 "Schedule of Activities" as follows:

- Weight will be taken ***in duplicate*** throughout the trial at approximately the same time of day, after voiding (ie, 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 (eg, 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 monthly and the record of scale accuracy must be sent to the sponsor at the end of the trial.

7.5. 12-Lead Electrocardiogram

Single, supine 12-lead ECG will be obtained at the pre-defined nominal time points outlined in "Schedule of Activities". 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 ECG collection.

- 12-lead ECGs should be performed after the subjects have 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 Screening visit (V1) ECG should be transmitted to the central vendor for reading and interpretation. This screening ECG will serve as the "baseline" ECG for comparison. All ECGs collected during the trial (planned and unplanned) 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.

If a subject experiences a non-fatal myocardial infarction after randomization, a new baseline ECG should be performed between 6 and 12 weeks following the myocardial infarction at an unplanned visit if necessary.

Subject demographic information will be made available to the central reading facility and the central reading facility will provide results on heart rate (BPM), overall interpretation, rhythm type, and heart rate intervals PR, QRS, QT, QTcB, and QTcF (msec), along with any comments.

7.6. Review of Self-Monitoring Glucose Logs

The site must review and assess the glucose values recorded on the self-monitoring glucose logs completed by the subjects at **each** site visit subsequent to the Day 1 visit (V2). For details on the treatment of glycemic control see Section 5.5.1.

7.6.1. Review of Hypoglycemia Assessment Logs

The site must review the hypoglycemia logs completed by the subjects at **each** site visit subsequent to the Day 1 visit (V2). Based on this information, an assessment of any symptomatic occurrence of hypoglycemia must be undertaken and appropriate decisions should be made by the investigator or the treating physician. For details on the treatment of glycemic control see Section 5.5.1.

7.6.2. Management of Hypoglycemia

Subjects will be instructed to check fingerstick glucose when they have symptoms consistent with hypoglycemia such as hunger, headache, dizziness, light headedness, sweating, palpitations, tachycardia, tremulousness, irritability, blurred vision, and disorientation. Subjects should be instructed to call the site should these symptoms occur and/or worsen before next visit, see Section 6.1.1.

Any episode of hypoglycemia must be captured on the HA eCRF. For definition of hypoglycemic episode and severity categorization, refer to Section 7.6.3 below.

7.6.3. Definition and Severity Categorization of Hypoglycemic Events

Based on review of the subject completed hypoglycemia logs at each outpatient visit to the site, the investigator must assess the glucose values as well as any symptoms documented. Each hypoglycemic event must be characterized with respect to severity and type.

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.

7.6.4. Guidance on Adverse Events Related to 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 fingerstick or plasma 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 8.1).

7.7. Sitting Blood Pressure and Pulse Rate

Triplicate measurement of sitting blood pressure and pulse rate should be performed using an automated oscillometric device at all time points noted in the Schedule of Activities. 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 in triplicate for subjects:

- 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.

7.8. Postural (Orthostatic) Blood Pressure and Pulse Rate

On the Day 1 visit (V2), Week 6 visit (V3) and Week 26 visit (V6), duplicate measurements of supine and standing blood pressure and pulse rate will be taken in order to evaluate postural changes in blood pressure and pulse rate. These measurements will be in addition to the sitting blood pressure and pulse rate measurements taken on these clinic visits and described above. Measurement of postural blood pressure and pulse rate will also occur at the Glycemic Rescue Visit.

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

First supine measurements:

- 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).

Second standing measurements:

- After the duplicate supine measurements have been performed, 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 performed 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.

7.9. Laboratory Studies

The tests outlined in Table 4 will be performed at the pre-specified time points outlined in the SOA following an overnight fast of at least 10 hours (except water). The FPG and HbA1c results from the central laboratory will be masked after randomization **through the initial 18 weeks of the trial** for both the sponsor and investigative site unless the results meet pre-specified glycemic rescue alert criteria as provided in Section 5.5.1. A confirmatory plasma glucose value from the central lab on a new plasma sample will be required to make a final determination as to whether a subject meets the criteria for glycemic rescue therapy. For all alerts that meet rescue criteria, the central laboratory will do a confirmatory test. If it is confirmed that a subject meets glycemic rescue criteria, FPG and HbA1c will be unmasked for the remainder of the trial. Following Week 18, HbA1c and FPG results will be reported to the investigative sites. Additionally, during the first 18 weeks of the study, the central laboratory will also unmask any FPG ≤70 mg/dl (3.9 mmol/L) only at that visit.

Table 4. Clinical/Safety-Related Laboratory Tests

Hematology	Chemistry	Urinalysis [b]	Others
Hemoglobin Hematocrit RBC Count Platelet Count WBC Count Total Neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Serum Creatinine eGFR (using MDRD equation) Ca^{++} (total) Na^{+} K^{+} Cl^{-} Total CO_2 (Bicarbonate) Mg^{++} Phosphate Uric Acid AST (SGOT) ALT (SGPT) Alkaline Phosphatase Total bilirubin Direct (conjugated) bilirubin [a] Indirect (unconjugated) bilirubin [a] Albumin Total Protein	pH Protein (qual) Blood (qual) Ketones Leukocyte esterase Nitrites Microscopy [c]	*At Screening visit (V1) only:* - Fasting triglycerides/TSH *At selected visits only (refer to): Schedule of Activities):* -HbA1c -FPG - Urinary albumin/creatinine ratio [d] - Pregnancy tests (where applicable) - Lipid panel (ie, total cholesterol, HDL-C, LDL,-C triglycerides, non-HDL-C) [e]

[a] Both direct and indirect bilirubin measured only when total bilirubin is greater than upper limit of normal.
[b] Routinely collected urinalysis samples will be sent to the central laboratory for dipstick analysis and microscopy if needed, see [c]. Urinalysis should not be collected for a female subject who is menstruating.
[c] Microscopy performed by the central laboratory if dipstick 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 a urologist for appropriate work-up.
[d] Sample 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.
[e] If LDL-C is measured directly on a Day 1 sample, the central laboratory will perform direct LDL-C measurements on subsequent samples for that subject.

7.9.1. Lipid Panel

A fasting lipid panel will be collected at the times listed in the Schedule of Activities. The lipid panel will consist of the following measurements:

- Total cholesterol, LDL-C, HDL-C, non-HDL-C and triglycerides.

LDL-C will be calculated, using the Friedewald equation. If the triglycerides are over 400 mg/dL, the laboratory will measure LDL-C directly. Non-HDL-C will be calculated as (total cholesterol - HDL-C). If LDL-C is measured directly on a Day 1 sample, the central laboratory will perform direct LDL-C measurements on subsequent samples for that subject.

7.9.2. Urinary Albumin:Creatinine Ratio

A urine sample will be collected on site at the times listed in the 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 2 days of the visit.

7.10. Assessment of Infections

7.10.1. Urinary Tract Infections

Any subject presenting with symptoms considered to be a urinary tract infection should be recorded as having an adverse event of "urinary tract infection." The site should collect urine for microscopic analysis and culture performed by their local laboratory, but urine dipstick or routine urinalysis should not be performed by the site or local laboratory. 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 either empirically as per local practice or following results from the urine culture and sensitivity analysis. 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 and treatment provided, and this information should be recorded.

7.10.2. 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.

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

Subjects who discontinue study drug for eGFR discontinuation criteria (see Section 6.7.4) or renal-related adverse events should have a repeat performed 1 week after the End of Study or Early Termination visit. The out of range test(s) should continue to be repeated at intervals, as considered appropriate (eg, 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 (eg, >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 (eg, non-steroidal anti-inflammatory agents, fenofibrate, ACE inhibitors, diuretic agents, etc.), and clinical assessment of volume status (eg, measurement of orthostatic heart rate and blood pressure, and physical examination focused on assessment of volume status); additional evaluations, including renal ultrasound, dipstick and microscopic urinalysis (with culture and sensitivity if infection is considered possible), urine creatinine and electrolytes, should be performed, as clinically appropriate.

8. ADVERSE EVENT REPORTING

8.1. 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 (ie, 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 in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

8.2. 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 (or equivalent).

8.3. 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 (or equivalent).

8.4. Immediate Reporting of Adverse Events to the Sponsor

8.4.1. 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 another important medical event.

Refer to Table 5 for additional details regarding each of the above criteria.

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

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

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

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

8.5. Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 5. The investigator's assessment of causality is required for each adverse event. Refer to Table 5 for instructions in evaluating adverse events.

Table 5. 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 [including hospitalization for an elective procedure] for a	

	preexisting condition which has not worsened does not constitute a serious adverse event.); 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	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
to Sponsor's Product (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.)	

Sponsor Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory authorities, IRBs/IECs and investigators in accordance with applicable local laws and regulations.

8.6. 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 (or equivalent).

Events of clinical interest for this trial include:

1. An overdose of sponsor's product, as defined in Section 8.2 - Definition of an Overdose for This Protocol and Reporting of Overdose to the sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

8.7. 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 investigational study drug 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 investigational study drug 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**
The subject should *interrupt* investigational study drug. 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. If an etiology for the elevated ALT or AST and TBL levels is established and the abnormalities resolve, investigational study drug may be restarted with approval by the Sponsor. Otherwise, the subject should discontinue treatment with investigational study drug. Note: Laboratory assessments prescribed in the Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials may be sent locally in emergent cases and to support subject compliance with the necessary evaluations. Subjects

unwilling to undergo the prescribed testing should be discontinued from treatment with investigational study drug.

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 (eg, fever, eosinophilia, right upper quadrant pain, dark urine, fatigue, etc.)

The subject should *interrupt* investigational study drug.

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

Initiate evaluation for potential causes. See Section II below.

Repeat ALT and AST tests at appropriate intervals, initially approximately 2-times per week, until resolution or return to baseline.

If an etiology for the elevated liver enzymes is established (eg, active hepatitis, cholecystitis, biliary obstruction), investigational study drug may be restarted with approval by Pfizer or designee. Otherwise, the subject should discontinue treatment with investigational study drug.

Note: Local laboratory assessments can be used to support compliance with the repeat testing procedure described above if required. Subjects unwilling to undergo repeat ALT and AST testing at the frequency recommended above should be discontinued from treatment with investigational study drug.

C) Subject has:

ALT or AST ≥3X and <8X ULN

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* study drug.

Initiate evaluation for potential causes. See Section II below.

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

If **ALT or AST ≥3X ULN with TBL ≥2X ULN,** then interrupt investigational study drug and see "*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 (eg, fever, eosinophilia, right upper quadrant pain, dark urine, fatigue, etc.), then interrupt investigational study drug and monitor as described in 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 (eg, every other week) until the subject's ALT and AST levels are within normal limits or are similar to baseline.

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

If **ALT or AST ≥5X ULN** after 2 weeks, *discontinue investigational study drug.*

If **ALT or AST remain elevated** (≥3X and <5X ULN) but stable, the frequency of retesting can decrease (eg, 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 (eg, 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 to undergo repeat ALT and AST testing at the frequency defined above should be discontinued from treatment with investigational study drug.

In summary, subjects should be discontinued from investigational study drug 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 (eg, 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 (eg, 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 (eg, autoimmune disorder, cancer, Gilbert's syndrome, obesity, Wilson's disease, Nonalcoholic steatohepatitis (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 (eg, 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.

8.8. Serious Adverse Events Exempt from Expedited Reporting

Potential pre-specified cardiovascular SAEs will be submitted for adjudication to an independent EAC (see Section 7.1 for details).

The following potential cardiovascular SAEs will not be subject to expedited reporting (ie, if reported as related to study drug by the investigator), unless and until the event is reviewed by the EAC and found not to meet the specified criteria in the EAC 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 EAC 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 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 E-DMC unblinded to treatment as part of the overall assessment of safety for ertugliflozin. Based upon their regular review of unblinded safety results, the E-DMC is empowered by the E-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 EAC not to meet the endpoint criteria (for the pre-specified events of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina) in the EAC 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 Pfizer or designee receives notification from the EAC that the event does not meet the endpoint criteria.

9. DATA ANALYSIS/STATISTICAL METHODS

Methodology for summary and statistical analyses of the data collected in this study are outlined here and further detailed in a statistical analysis plan, which will be dated and maintained by the sponsor. The statistical analysis plan may modify what is outlined in the protocol where appropriate; however, any major modifications of the endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The cardiovascular safety of ertugliflozin will be assessed in two stages. Stage 1 will consist of a meta-analysis of MACE plus events across the Phase 2 and Phase 3 development program with the majority of events expected to come from this trial. Stage 2 will consist of an analysis of MACE and secondary endpoints [eg, CV death or hospitalization for heart failure (composite), CV death (individual component), and the renal composite] in this trial. The two doses of ertugliflozin (5 and 15 mg) will be pooled for the purpose of all these analyses.

The primary objective for the Stage 1 across-program meta-analysis will be addressed by testing the hypotheses H0:HR≥1.8 versus H1:HR<1.8 for the MACE plus endpoint; the primary Stage 2 analysis (assessed within this study) will be addressed by testing the hypotheses H0:HR≥1.3 versus H1:HR<1.3 for the MACE endpoint. For these analyses, the HR represents the risk of ertugliflozin relative to a non-ertugliflozin comparator group at Stage 1 and relative to placebo at Stage 2 as measured by the hazard ratio.

Stage 1 of the trial uses a group sequential design with up to two analyses: an interim analysis and a final analysis. The Stage 1 interim analysis will take place at the later of 1) the time at which at least 130 adjudicated MACE plus events have accrued throughout the Phase 2 and Phase 3 development program or 2) the approximate time at which all necessary data are available to support the filing of ertugliflozin. This analysis will assess the hazard ratio for the MACE plus endpoint with respect to the 1.8 non inferiority margin. If the first analysis is conducted with less than 173 MACE plus events, then a second analysis (the final analysis for Stage 1) will take place, if necessary (ie, if the non-inferiority margin of 1.8 is not met in the first analysis), at the time at which at least 173 MACE plus events have accrued, and the appropriate alpha spending will be determined from an O'Brien-Fleming type spending function. If the first analysis is conducted with 173 or more MACE plus events, then that will constitute the only analysis for Stage 1, and the full alpha of 0.025 (1-sided) will be utilized.

For these Stage 1 analyses, using an O'Brien-Fleming type alpha spending function, and analyses at 130 and 173 adjudicated MACE plus events, the meta-analysis will have approximately 95% power to demonstrate non-inferiority of ertugliflozin to a non-ertugliflozin comparator group when there is truly no difference between treatments (HR=1.0) using the non-inferiority margin of 1.8 and testing at the overall one-sided alpha level of 0.025.

Stage 2 of the trial uses a group sequential design with up to two analyses: an interim analysis and a final analysis. The Stage 2 interim analysis and the final analysis are planned to occur when approximately 714 and 939 adjudicated MACE events have accrued in this study. These analyses will assess the hazard ratio for the MACE endpoint with respect to the 1.3 non-inferiority margin. If non-inferiority is established for the primary MACE endpoint, then tests of superiority on the secondary endpoints of CV death or hospitalization for heart failure (composite), CV death (individual component), and the renal composite will also be performed in a sequential manner. If any of the first three tests in this four-step testing sequence are unsuccessful at the interim analysis, the study may be continued to the final analysis (depending on the result of futility assessment).

For the primary Stage 2 analyses, using an O'Brien-Fleming type alpha spending function and analyses at approximately 714 and 939 adjudicated MACE events, the study will have approximately 96% power to demonstrate non-inferiority of ertugliflozin to placebo when there is truly no difference between treatments (HR=1.0) using the non-inferiority margin of 1.3 and testing at the overall one-sided alpha level of 0.025.

The accrual of 714 MACE events (ie, an information fraction of about 76%) was selected as the time point for interim assessment as the power to demonstrate non-inferiority at the interim with this number of events is >80% and the estimated corresponding number of CV deaths and heart failure hospitalizations (ie, 442 events) provides approximately 70% power to detect a 25% risk reduction in this secondary endpoint at the interim.

With two enrollment periods of 19 months each and assuming an event rate of 3.5% per annum for MACE, a total of approximately 8000 subjects (about 4000 per enrollment cohort) randomized in a 1:1:1 ratio to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo will be sufficient to accrue approximately 714 MACE events within approximately 5.0 years and approximately 939 MACE events within approximately 6.1 years from the start of this study. These calculations assume that subjects will withdraw from the study at a rate of 5% per annum.

Power for Secondary Hypotheses

For the Stage 2 analyses of secondary endpoints, using an O'Brien-Fleming alpha-spending approach and assuming accrual of at least 442 and 582 composite events of cardiovascular death or hospitalization for heart failure at the interim and final analysis respectively, the study will have approximately 90% power to demonstrate superiority of ertugliflozin to placebo on the composite of cardiovascular death or hospitalization for heart failure when the true HR=0.75. Moreover, assuming accrual of at least 287 and 377 cardiovascular death

events at the interim and final analysis respectively, the study will have approximately 83% power to demonstrate superiority of ertugliflozin to placebo on cardiovascular death when the true HR=0.725. With accrual of at least 144 and 190 renal composite events at the interim and final analysis respectively, the study will have approximately 79% power to demonstrate superiority of ertugliflozin to placebo on the renal composite endpoint when the true HR=0.65.

9.1.1. Sample Size for Insulin with or without Metformin Add-on Glycemic Sub-Study:

The sub-study is powered to demonstrate superiority of ertugliflozin compared with placebo in reducing HbA1c from Baseline to Week 18. It is estimated that a minimum of 450 subjects will be enrolled into the sub-study. The sub-study enrollment will not be allowed to exceed 50% of the overall trial sample size. The final determination of inclusion in the sub-study will be based on a programmatic assessment of the sub-study criteria.

In two recent studies of another SGLT2 inhibitor (dapagliflozin) in subjects with type 2 diabetes receiving high doses of insulin, estimates of the standard deviation of the change from baseline in HbA1c after 24 weeks ranged up to a maximum of 0.98%.[15,16]. Therefore, a standard deviation of 1.0% was taken as a conservative estimate for sample size calculations.

Assuming a standard deviation of 1.0% and a lost to follow up rate of 10%, a sample size of 450 subjects (150 per arm) will provide approximately 98% power to detect a difference of 0.5% in the reduction of HbA1c from Baseline to Week 18 between ertugliflozin and placebo using a 2-sided 0.05 alpha level test.

9.1.2. Sample Size for SU Monotherapy Add-on Glycemic Sub-Study:

The primary endpoint for the sub-study is the HbA1c change from Baseline to Week 18. It is estimated that approximately 170 subjects will be enrolled into the sub-study. The final determination of inclusion in the sub-study will be based on a programmatic assessment of the sub-study criteria.

Assuming a standard deviation of 1.0%, a lost to follow up rate of 10%, and a sample size of 170 subjects (~56 per arm), the power to detect a between treatment difference of 0.6% will be approximately 85% using a 2-sided alpha level of 0.05.

9.1.3. Sample Size for Metformin with SU Add-on Glycemic Sub-Study

The primary endpoint for this sub-study is the HbA1c change from Baseline to Week 18. It is estimated that at least 260 subjects will satisfy the criteria for inclusion in this sub-study. Assuming a standard deviation of 1.0% and a lost to follow up rate of 10%, a sample size of 260 subjects (~86 per arm) will provide approximately 96% power to detect a difference of 0.6% in the reduction of HbA1c from Baseline to Week 18 between ertugliflozin and placebo using a 2-sided 0.05 alpha level test.

As there is no separate randomization stratum for the metformin with SU sub-study, this sub-study will consist of a sub-group of subjects from the “main cardiovascular study”

stratum. The determination of inclusion in the sub-study will be based on a programmatic assessment of the sub-study criteria; see Section 3.4.

9.2. Primary Cardiovascular Endpoints Analysis

The two doses of ertugliflozin will be pooled for the analysis of cardiovascular endpoints. The analyses described below will be performed at the interim analysis and at the end of the trial.

The Stage 1 meta-analysis population will include all randomized subjects who have taken at least one dose of investigational product across the Phase 2 and 3 development program. The Stage 2 non-inferiority analysis population will include all randomized subjects who have taken at least one dose of investigational product in this study. For both stages, subjects will be analyzed in the group to which they were assigned by IVRS, regardless of the actual treatment received and only events confirmed by the Endpoint Adjudication Committee will be included in the analysis. For Stage 1, all confirmed MACE plus events will be included in the primary analysis. For Stage 2, confirmed MACE events occurring between randomization and 365 days after the last dose of study treatment will be included in the primary non-inferiority analysis.

The MACE plus and MACE endpoints will be analyzed using a stratified Cox proportional hazards model including treatment group as a covariate. For the Stage 1 meta-analyses, the Cox model will include "Study" as a stratification factor with the following three levels: cardiovascular study, placebo-controlled non-cardiovascular studies, and active-controlled non-cardiovascular studies. For the Stage 2 analyses, the Cox model will include "Cohort" as the stratification factor with the following levels: Cohort 1 (subjects randomized between December 2013 and July 2015) and Cohort 2 (subjects randomized in 2016 and beyond). A test of non-inferiority at the one-sided 0.025 significance level will be performed based on the Cox model. The upper bound of the alpha-adjusted two-sided confidence interval (CI) for the hazard ratio (HR) (ertugliflozin to a non ertugliflozin comparator group or placebo) will be calculated using an O'Brien-Fleming alpha spending function and compared with the appropriate non-inferiority margin (1.8 or 1.3).

Kaplan-Meier curves for the distribution of time to MACE and MACE plus will also be provided for each of the three treatment groups.

Subjects without cardiovascular events will be censored at the earliest of the study cut-off date, last contact date, or end of the applicable analysis ascertainment window (eg, 365 days after the last dose for primary Stage 2 non-inferiority analyses).

9.3. Secondary Endpoints Analysis

Secondary time-to-event endpoints (eg, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, hospitalization for heart failure, cardiovascular death, the composite of cardiovascular death or hospitalization for heart failure, the renal composite, and all-cause mortality) will be analyzed using Cox proportional hazards models with the same model terms as those included for the primary endpoint. A point estimate and two-sided nominal 95% confidence interval for the hazard ratio will be calculated based on the Cox model for

each endpoint. Kaplan-Meier methodology will be used to estimate event rates over time for each treatment group.

If non-inferiority at the 1.3 margin is established for the primary MACE endpoint based solely on this study, then tests of superiority on the secondary endpoints of cardiovascular death or hospitalization for heart failure (composite), cardiovascular death (individual component), and the renal composite will also be performed. The population for superiority testing will include all randomized subjects and include all confirmed events, including those occurring more than 365 days following discontinuation of investigational product. Superiority tests will be implemented by comparing the upper bound of the appropriate alpha-adjusted two-sided CI to 1.0.

In order to control the Type I error rate across multiple hypotheses in Stage 2, a four-step hierarchical testing sequence for the pooled ertugliflozin group versus the placebo group will be utilized as follows:

1. Non-inferiority for MACE;
2. Superiority for cardiovascular death or hospitalization for heart failure (composite);
3. Superiority for cardiovascular death (individual component);
4. Superiority for composite of renal death, renal dialysis/transplant, or ≥2x increase in baseline serum creatinine.

If the result of the test at any step of the sequence is not statistically significant, then testing will stop so that tests further down in the sequence will not be conducted, and the corresponding null hypotheses will not be rejected. The alpha spending to be utilized for the interim and final analyses of the primary and secondary endpoints is described in Section 9.7.

Recurrent MACE and recurrent cardiovascular death or hospitalization for heart failure will also be analyzed using Anderson-Gill models. A point estimate and two-sided 95% confidence interval for the risk ratio (ertugliflozin compared to placebo) will be calculated based on the model for each endpoint. These analyses of recurrent events will be considered exploratory and only performed at the end of the study.

9.4. Other Secondary Endpoints Analysis

Continuous endpoints (HbA1c, FPG, body weight, systolic blood pressure and diastolic blood pressure) will be analyzed using a constrained longitudinal data analysis (cLDA) model including fixed effects for treatment (categorical), visit (categorical), and treatment by visit interaction. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. No explicit imputation of missing assessments will be performed. The treatment difference in terms of mean change from baseline to the relevant

time points of interest will be estimated and tested from this model using least-squares means and 95% confidence intervals. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make proper statistical inference. Descriptive and graphical summaries by treatment group and time point will also be presented. Other continuous endpoints will be summarized with descriptive statistics by treatment and time.

Dichotomous endpoints such as the proportion of subjects having an HbA1c <7% (53 mmol/mol) at specified time points, will be analyzed using a logistic regression model with terms for treatment (categorical) and baseline HbA1c (continuous). Summary measures from the analysis will include the odds ratio and 95% confidence interval for the odds ratio. Other dichotomous endpoints will be summarized descriptively with numbers and percentages by treatment and time.

9.5. Analysis of Laboratory and Biomarker Endpoints

9.5.1. Albuminuria

Change from Baseline in the urinary albumin:creatinine ratio stratified by albuminuria category at baseline (normoalbuminuria, microalbuminuria and macroalbuminuria), will be compared between ertugliflozin and placebo-treated subjects. In addition, albuminuria progression, defined as a change from normoalbuminuria to either microalbuminuria or macroalbuminuria or from microalbuminuria to macroalbuminuria, will be assessed comparing the baseline data to the data collected according to the following definitions:

- Normoalbuminuria: <30 mg/g (albumin:creatinine ratio).
- Microalbuminuria: ≥30mg/g to ≤300 mg/g (albumin:creatinine ratio).
- Macroalbuminuria: >300 mg/g (albumin:creatinine ratio).

Regression of albuminuria will be defined as subjects noted to have an improvement in albuminuria defined as moving from macroalbuminuria to microalbuminuria (or normoalbuminuria) or from microalbuminuria to normoalbuminuria.

9.6. Safety Analysis

The safety analysis population will consist of all randomized and treated subjects, ie, all randomized subjects who received at least one dose of investigational product in this trial.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify all AEs with respect to system organ class and preferred term. Summaries of AEs will include treatment-emergent AEs according to treatment group.

Two approaches will be used for handling safety data occurring after the initiation of glycemic rescue therapy. The first approach will exclude all data following the initiation of rescue, in order to avoid the confounding influence of the rescue therapy. The second

approach will include data following the initiation of rescue therapy. For the overall study analyses, the "including rescue" approach will be considered primary for all safety endpoints as, after Week 18, subjects are treated to standard of care, and there is no longer glycemic rescue. For glycemic sub-study analyses, the "including rescue" approach will be considered primary for analyses of SAEs and discontinuations of study drug due to AEs, and the "excluding rescue" approach will be considered primary for all other endpoints. Descriptive statistics will be used to summarize results and changes from Baseline in clinical laboratory tests, vital signs, and ECGs.

Furthermore, a 3-tier approach will be used to summarize AEs. Tier-1 consists of AEs of special clinical interest and will include AEs or collections of AEs related to urinary tract infection, genital mycotic infection, symptomatic hypoglycemia and hypovolemia. Where available, standard MedDRA queries may be used to pool different AE terms that are related to the Tier-1 AEs. The precise AE terms that will contribute to the Tier-1 endpoints will be determined prior to unblinding. For these events, the percentage of subjects with incident AE, the risk difference, its 95% confidence interval, and p-value will be provided. The confidence intervals and p-values are not adjusted for multiplicity and therefore must be considered accordingly. Tier-2 AEs are those that are not Tier-1, but that occur in a pre-specified minimum number of subjects in any treatment arm. For the overall study, this requirement will be at least 0.5% of subjects in any treatment arm, and for each sub-study, the requirement will be at least 4 subjects in any treatment arm. The cut-off of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and so adds little to the interpretation of potentially meaningful differences. For these events, the percentage of subjects with incident AE, the risk difference and its 95% confidence interval will be provided. Tier-3 AEs are all other AEs (neither Tier-1 nor Tier-2). For Tier-3 AEs, only within-group incidence proportions will be tabulated.

9.7. Cardiovascular Endpoints Interim Analyses

Each stage of the study uses a group sequential design with planned interim analyses as described below.

Stage 1

The first interim analysis will be conducted at the later of 1) the time at which a minimum of 130 adjudicated MACE plus events have accrued throughout the Phase 2 and Phase 3 development program or 2) the approximate time at which all necessary data are available to support the filing of ertugliflozin. The purpose of this interim analysis is to provide data for a meta-analysis of cardiovascular events that will support the initial regulatory submissions and rule out a hazard ratio of 1.8 (an 80% increase in cardiovascular risk relative to the non-ertugliflozin comparator group). If necessary (ie, if the first interim analysis is conducted with less than 173 MACE plus events and fails to rule out an HR>1.8), a subsequent final Stage 1 analysis will be conducted after at least 173 adjudicated MACE plus events have accrued. For each of these analyses, the two-sided adjusted CI for the HR will be calculated using an O'Brien-Fleming spending function to preserve the overall Type I

error rate of 2.5% with respect to the non-inferiority margin of 1.8. The analysis at approximately 130 MACE plus events corresponds to an information fraction of approximately 75% with respect to the Stage 1 MACE plus analyses and the amount of alpha to be spent for this analysis is about 1.0% (one-sided). If at either of these looks, the upper bound of the two-sided adjusted CI is <1.8, this result will be communicated to the E-DMC by an independent statistician(s) and may subsequently be submitted to regulatory authorities. If, on the other hand, the upper bound of the adjusted CI is >1.8 at both of these analyses, then the study may be stopped for futility.

Stage 2

Once the 1.8 threshold has been met, the study will continue to Stage 2. An interim analysis will take place when approximately 714 MACE events have accrued in this study. The purpose of this analysis will be to rule out an HR of 1.3 for MACE and to sequentially test for superiority on the secondary endpoints of cardiovascular death or hospitalization for heart failure (composite), cardiovascular death (individual component), and the renal composite. If necessary (ie, if the interim analysis fails to rule out an HR >1.3 or to achieve superiority on both of the secondary CV endpoints), the final analysis will take place after accrual of approximately 939 MACE events. For the primary non-inferiority analysis of MACE, the two-sided adjusted CI for the HR will be calculated using an O'Brien-Fleming spending function to preserve the overall Type I error rate of 2.5% with respect to the non-inferiority margin of 1.3. The analysis at approximately 714 MACE events corresponds to an information fraction of approximately 76%, and the amount of alpha to be spent for this analysis is about 1.0% (one-sided). The subsequent secondary hypothesis tests will utilize a similar O'Brien-Fleming alpha spending approach with a 2.0% two-sided alpha spend for each hypothesis at the interim. If at the end of the study, the upper bound of the two-sided adjusted CI is <1.3 for MACE, the study will be considered to have met its primary objective of demonstrating the non-inferiority of ertugliflozin as compared to placebo with respect to cardiovascular safety. Details regarding alpha spending and power for the primary analyses at each potential analysis time are described in Table 6 below.

Table 6. Alpha Adjusted Confidence Interval and Power for Primary Analyses

Stage	Analysis (within Stage)	Events (confirmed by adjudication)	Alpha for adjusted confidence interval (one-sided)	Power to Demonstrate Non-Inferiority*
1 Phase 2 and 3 Meta-analysis	1 Interim	130 MACE plus	1.0%	79.5%
	If the upper bound at interim analysis is ≥1.8 for MACE plus			
	2 Final	173 MACE plus	2.2%	95.1% (cumulative)
Once the 1.8 threshold has been met, the study will continue to Stage 2				
2 Study P004/B1521021	1 Interim	714 MACE	1.0%	83.8%
	If the upper bound at interim analysis is ≥1.3 for MACE			
	2 Final	939 MACE	2.2%	96.4% (cumulative)

* Power under HR=1.0

Interim Futility Analysis for Secondary Endpoints

Furthermore, if non-inferiority on MACE (1.3 margin) is achieved at the Stage 2 interim analysis, but superiority on cardiovascular death or heart failure hospitalization is not achieved at that same analysis, the conditional power for achieving superiority at the subsequently planned analysis will be computed by an appropriately firewalled cardiovascular analysis team and provided to the E-DMC for assessment as described in the Data Access Plan. Depending on the results of this conditional power evaluation, the study may be continued in order to use the remaining alpha to conduct further superiority testing of the secondary endpoints. Under such a scenario, the study could be continued up to the pre-specified maximum number of events (ie, approximately 582 composite events of cardiovascular death or heart failure hospitalization and approximately 377 events of cardiovascular death). On the other hand, if the conditional power for superiority is not high enough, the study may be terminated having achieved the primary objective of demonstrating non-inferiority for MACE in Stage 2. The relevant decision criteria for assessing the conditional power for superiority will be included in the Statistical Analysis Plan. The assessment of conditional power for superiority will be considered as a non-binding futility assessment for the secondary endpoints.

Stage 2 Type I Error Rate Control

The overall Type I error rate in Stage 2 will be strongly controlled using a combination of fixed sequential testing across endpoints and alpha spending approaches across analysis time points.[17,18] The following chart summarizes the alpha levels that will be utilized for each endpoint at each analysis time point in Stage 2. The fixed sequential testing sequence of the endpoints is described in Section 9.3. Note that alpha allocated to the secondary superiority tests at the interim will be considered to be consumed even if the test is not conducted due to the hierarchical testing sequence. Also note that if the primary non-inferiority test is successful at the interim, but the study continues to the final analysis for the secondary superiority tests, a supportive analysis of the primary non-inferiority hypothesis will be conducted at the final analysis time point using the full alpha level of 0.025. Similarly, if the secondary superiority test for the composite of CV death and hospitalization for heart failure is successful at the interim but the study continues to the final analysis (ie, the secondary superiority test for CV death is not successful at the interim), a supportive analysis of the secondary superiority hypothesis for CV death and hospitalization for heart failure will be conducted at the final analysis time point using the full alpha level of 0.05.

Sequence Number*	Endpoint (test)	Alpha for adjusted confidence interval	
		Interim Analysis	**Final Analysis**
1	MACE (non-inferiority)	1% (one-sided)	2.2% (one-sided); if test not successful at interim
			2.5% (one-sided); if test successful at interim
2	Cardiovascular death/hospitalization for heart failure (superiority)	2% (two-sided)	4.4% (two-sided); if test not successful at interim
			5% (two-sided); if test successful at interim
3	CV death (superiority)	2% (two-sided)	4.4% (two-sided)
4	Renal composite (superiority)	2% (two-sided)	4.4% (two-sided)
*Note: If the result of the test at any step of the sequence is not statistically significant, then testing will stop so that tests further down in the sequence will not be conducted (and therefore not considered successful).			

The various possible actions to be taken based on the Stage 2 interim analysis results are summarized in the following table:

Scenario at Interim	Action
Primary test unsuccessful	Study continues to final analysis
Primary test successful and CV death/hospitalization for heart failure composite endpoint unsuccessful but not futile	Study continues to final analysis
Primary test successful and CV death/ hospitalization for heart failure composite endpoint futile	Study may be stopped for success on the primary objective and futility on the secondary superiority objectives
Primary test and CV death/ hospitalization for heart failure composite both successful; CV death unsuccessful	Study continues to final analysis
Primary test, CV death/ hospitalization for heart failure composite, and CV death all successful	Study may be stopped for success (regardless of the outcome for the renal composite)

The interim analyses will be performed by an independent team of statistician(s) and programmer(s) and will be reviewed by the E-DMC to determine whether excess risk with ertugliflozin relative to the non-ertugliflozin comparator group or to placebo (HR>1.8 or 1.3) may be ruled out. The results of the meta-analysis (Stage 1) will be submitted to regulatory authorities. Only upon request from or with agreement of regulatory authorities may the three glycemic sub-studies be analyzed and submitted while the main study is on-going.

9.8. Insulin with or without Metformin, SU Monotherapy Add-on and Metformin with SU Glycemic Sub-Study Analyses

Primary Efficacy Analyses: The primary analysis population for each sub-study will be the sub-study Full Analysis Set defined as all subjects randomized receiving those specific background treatments at baseline, who meet all sub-study inclusion criteria (eg, minimal

dose(s) and dose stable period),who have received at least one dose of investigational product and have at least one observation of HbA1c during the time of the sub-study, including baseline and post-baseline time points up to Week 18 inclusive. If subjects receive glycemic rescue therapy, the observations post rescue therapy will be excluded from efficacy analyses of the primary and secondary endpoints.

The primary endpoint of HbA1c will be analyzed using a constrained longitudinal data analysis (cLDA) model with the following fixed effects:

- Treatment (categorical);
- Visit (categorical);
- Treatment by visit interaction;
- Baseline eGFR;
- Metformin use (yes/no; applicable for insulin (with or without metformin) sub-study only).

This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. No explicit imputation of missing assessments will be performed. The treatment difference in terms of mean change from baseline to the primary time point of Week 18 will be estimated and tested from this model using least-squares means and 95% confidence intervals. The two-sided p-value will also be provided for testing the significance of the difference between treatment groups. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make proper statistical inference. Sensitivity analyses will be planned to assess the robustness of the primary model. Descriptive and graphical summaries by treatment group and time point will also be presented.

The two primary hypotheses, comparisons of each ertugliflozin dose to placebo, will be tested sequentially to control the overall Type I error rate at 0.05. The 15 mg dose will be tested first, and the 5 mg dose will be tested if and only if a statistically significant result is achieved for 15 mg.

Secondary Efficacy Analyses: The proportion of subjects achieving an HbA1c <7% (53 mmol/mol) at Week 18 will be analyzed using a logistic regression model with terms for treatment (categorical), metformin use (yes/no; applicable for insulin with or without metformin sub-study only), Baseline eGFR, and Baseline HbA1c (continuous). Summary measures from the analysis will include the odds ratio, 95% confidence interval for the odds ratio, and p-value for the comparison of treatment groups.

The secondary endpoints of fasting plasma glucose, body weight, and blood pressure will be analyzed separately by fitting constrained longitudinal data analysis models similar to that used for the primary endpoint. For the insulin with or without metformin sub-study, the change in insulin dose from Baseline to Week 18 will also be summarized.

Hypothesis testing in the insulin with or without metformin sub-study, the SU monotherapy sub-study and in the metformin with SU sub-study will be performed with a 2-sided alpha of 0.05. The Type I error rate will be controlled by following a fixed testing sequence. If the result of the test at any step of the sequence is not statistically significant, then testing will stop so that tests further down in the sequence will not be conducted, and the corresponding null hypotheses will not be rejected. All tests will be conducted at the 0.05 alpha level.

For each endpoint, there are two hypotheses: comparisons of each ertugliflozin dose to placebo. The 15 mg dose will be tested first, and the 5 mg dose will be tested if and only if a statistically significant result is achieved for 15 mg. Testing will advance to the next endpoint in the sequence if and only if a statistically significant result is obtained for both doses.

The endpoints will be tested in the following sequence:

1. Reduction of HbA1c from Baseline at Week 18.
2. Reduction of FPG from Baseline at Week 18.
3. Reduction of body weight from Baseline at Week 18.
4. Proportion of subjects achieving an HbA1c <7% (53 mmol/mol) at Week 18.
5. Reduction of systolic blood pressure from Baseline at Week 18.
6. Reduction of diastolic blood pressure from Baseline at Week 18.

9.9. Data Monitoring Committee

This study will use an E-DMC.

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the trial and a separate E-DMC Charter will describe the precise mandates of the E-DMC. The recommendations made by the E-DMC to alter the conduct of the trial will be forwarded to the sponsor for final decision. The DMC charter will specify the role and responsibilities of the E-DMC and also the contact individuals within the sponsor organization and the E-DMC responsible for communication between these organizations. The sponsor will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer/Merck or their agents will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs is accurate. The investigator and institution will allow Pfizer/Merck monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer/Merck and should not be made available in any form to third parties, except for authorized representatives of Pfizer/Merck or appropriate regulatory authorities, without written permission from Pfizer/Merck.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at the sponsor and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer/Merck, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed ICD, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, ICD, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer or its designee.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. In case of data transfer, Pfizer/Merck will maintain high standards of confidentiality and protection of subject personal data.

The ICD must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Informed Consent 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.

12.5. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.6. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer or its designee should be informed immediately.

In addition, the investigator will inform Pfizer or its designee immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all other Participating Countries

End of Trial in all other participating countries is defined as Database Lock.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer/Merck. In addition, the Pfizer/Merck retains the right to discontinue development of PF-04971729 at any time.

If a study is prematurely terminated or discontinued, Pfizer or its designee will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 28 days. As directed by Pfizer or its designee, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by the Sponsor

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

The sponsor has no objection to publication by investigator of any information collected or generated by investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected inventions, investigator will provide the sponsor an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to the sponsor at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. Collection and Management of Specimens for Future Biomedical Research

Scope of Future Biomedical Research

The DNA, plasma and serum specimens collected in the current trial will be used to study various causes for how subjects may respond to a drug. The DNA, plasma and serum specimens will be stored to provide a resource for future studies conducted by the sponsor focused on the study of biomarkers responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease.

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, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the sponsor or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

[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.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects at the first visit. If delayed, present consent at next possible subject visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens.

Subjects are not required to participate in Future Biomedical Research in order to participate in the main trial.

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 who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be withdrawn from the main study.

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other study 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 (eg, DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

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 study 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 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 study 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 study 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 (ie, 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 health authorities (eg, EMA, FDA), whereby this information would be directly transferred to the health authority.

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 (eg, 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-study. 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.

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 study. If medical records for the main study are still available, the investigator will contact Merck using the designated mailbox (clinical.specimen.management@merck.com) 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 study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory agencies to retain the main study 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.

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 agency 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 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.

Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-study 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 study 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 (eg, 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-study will not be used for any other purpose.

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 study 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 practices 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 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 (eg, 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.

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 studies 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.

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 study.

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 (ie, ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc) to be reassociated 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.

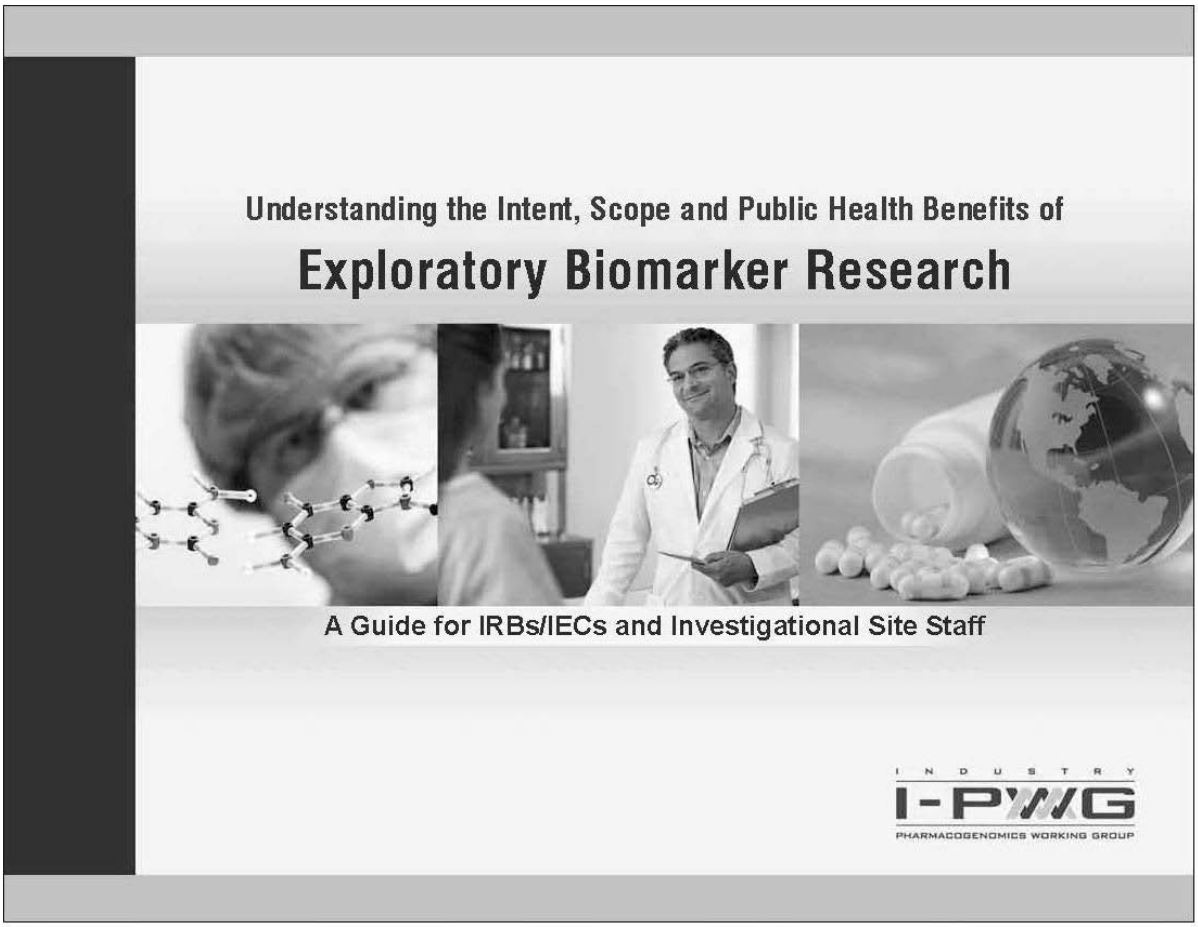
Self-Reported Ethnicity

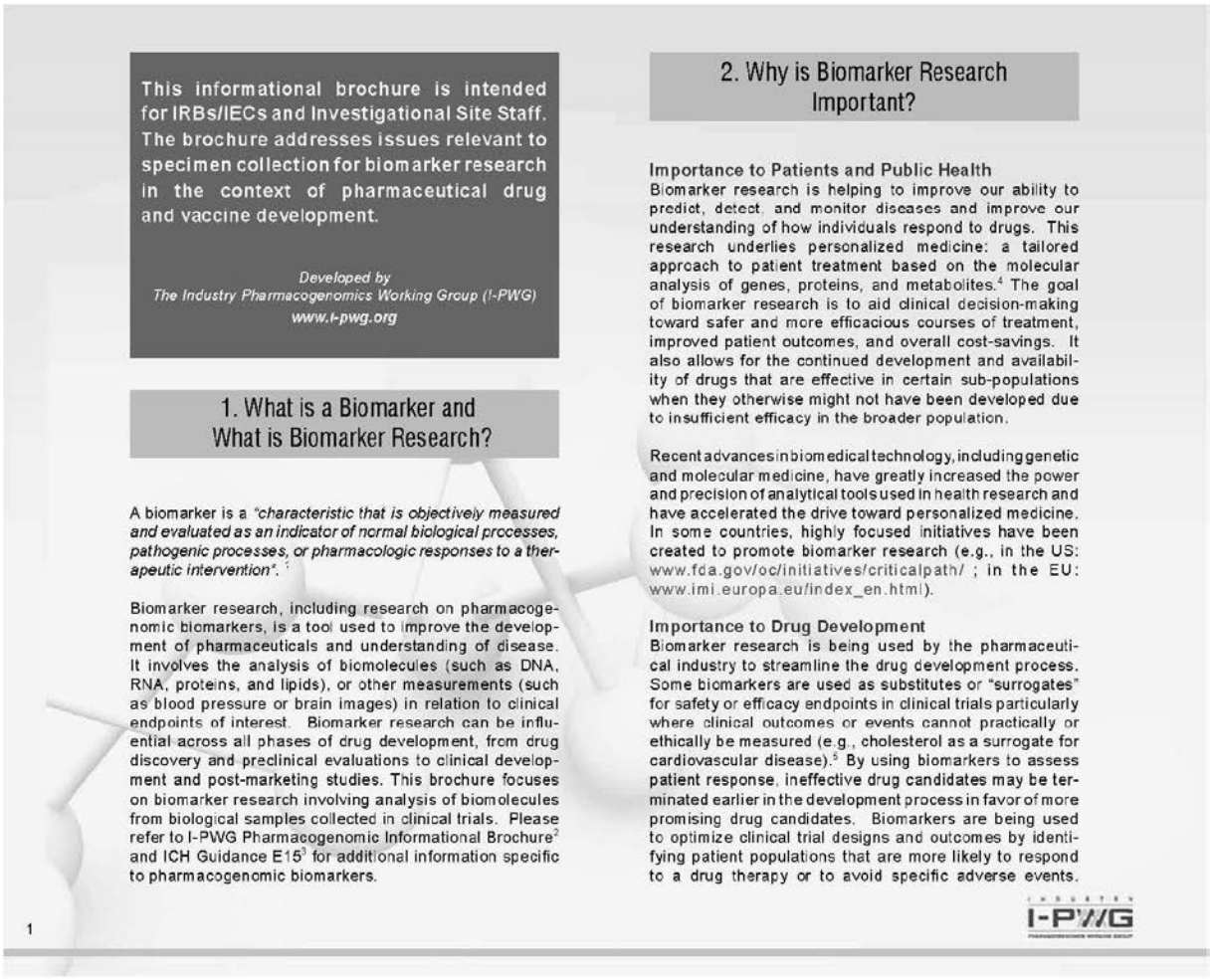
Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

Appendix 2. Biomarker Brochure





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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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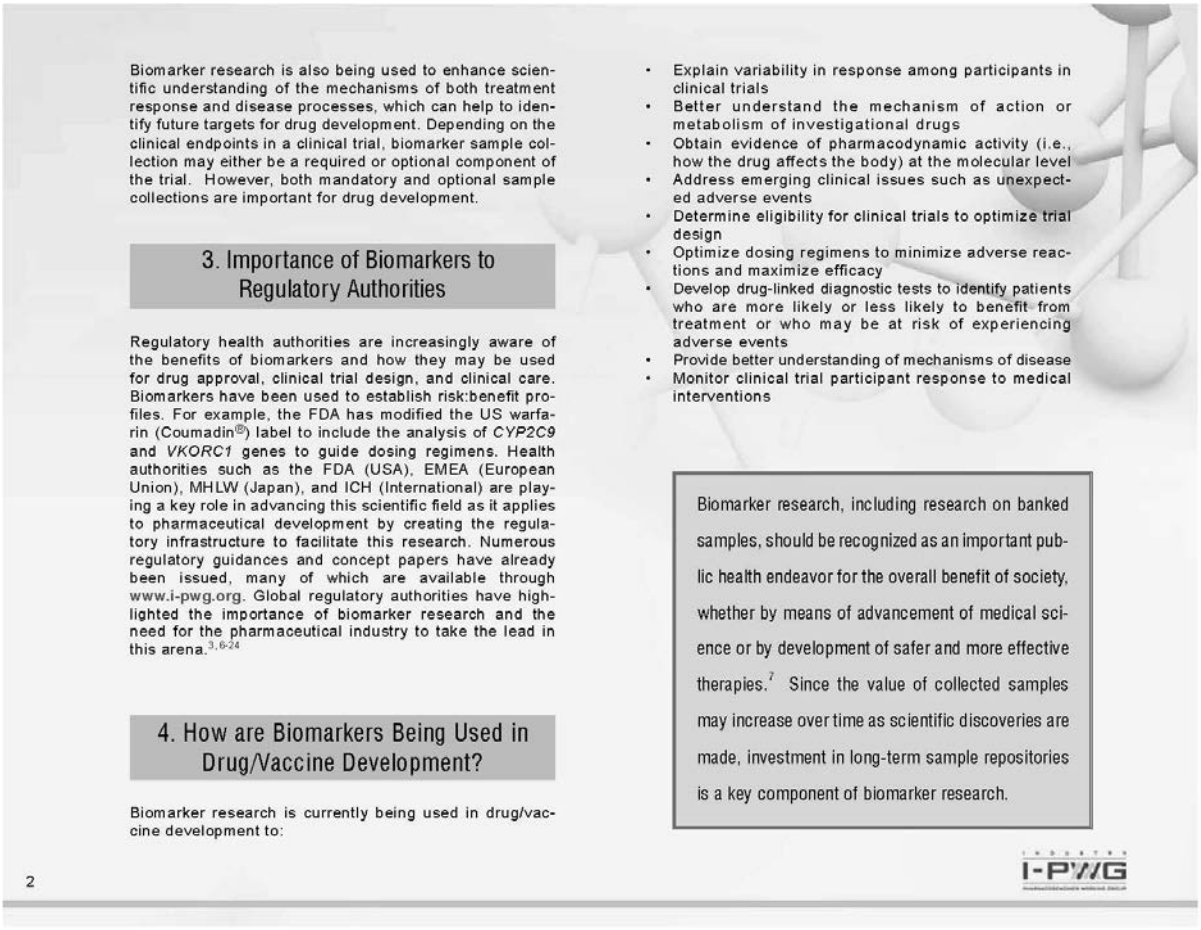

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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

3. Importance of Biomarkers to Regulatory Authorities

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

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

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

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

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

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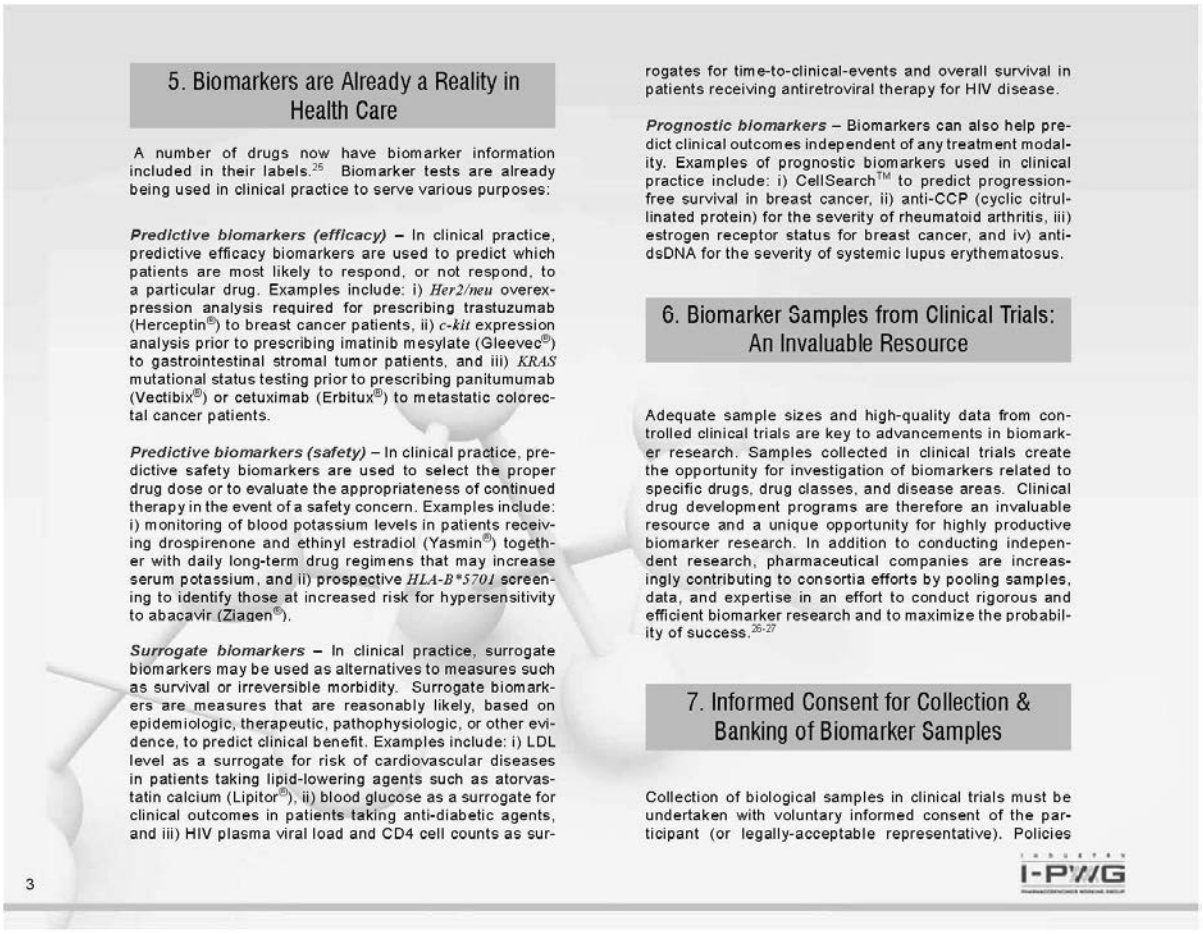

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[39]

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

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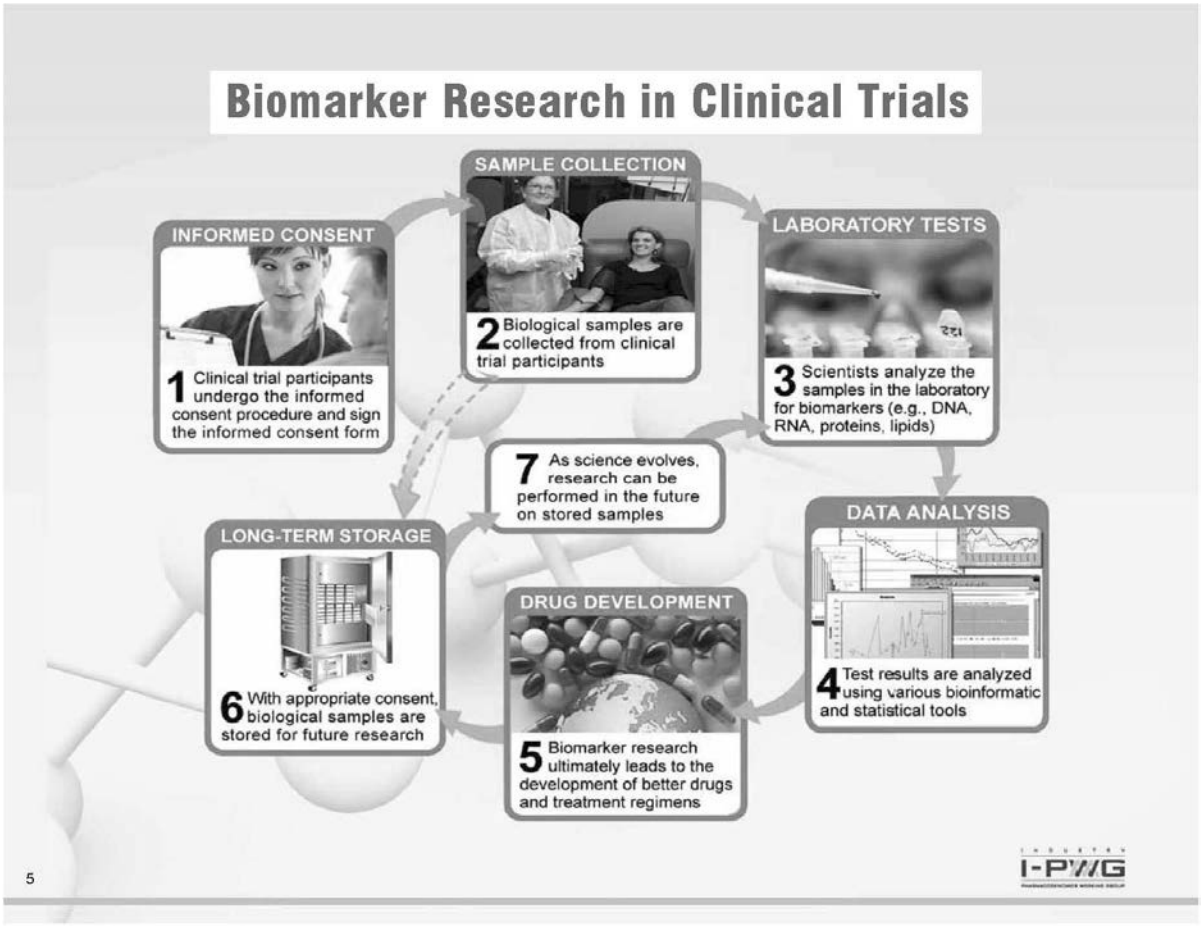

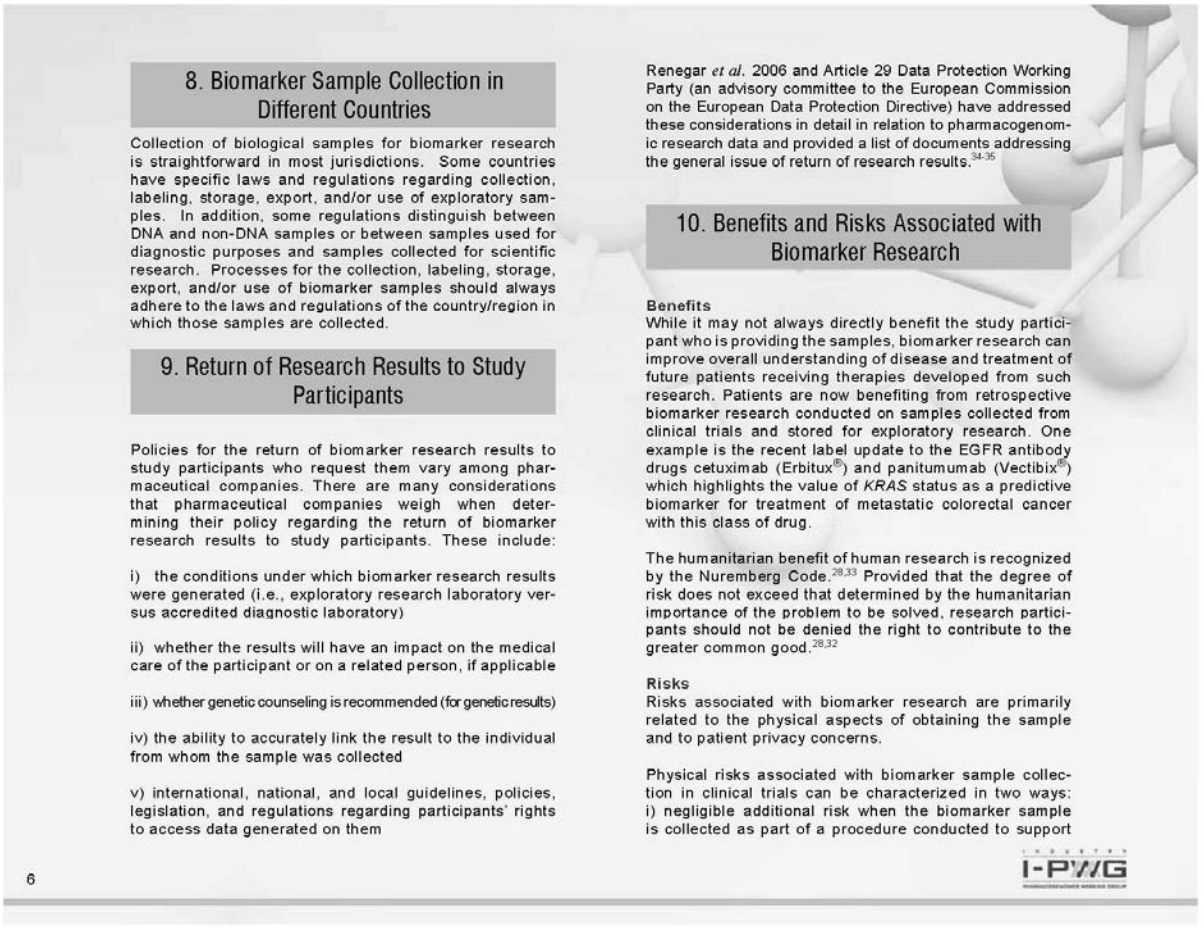

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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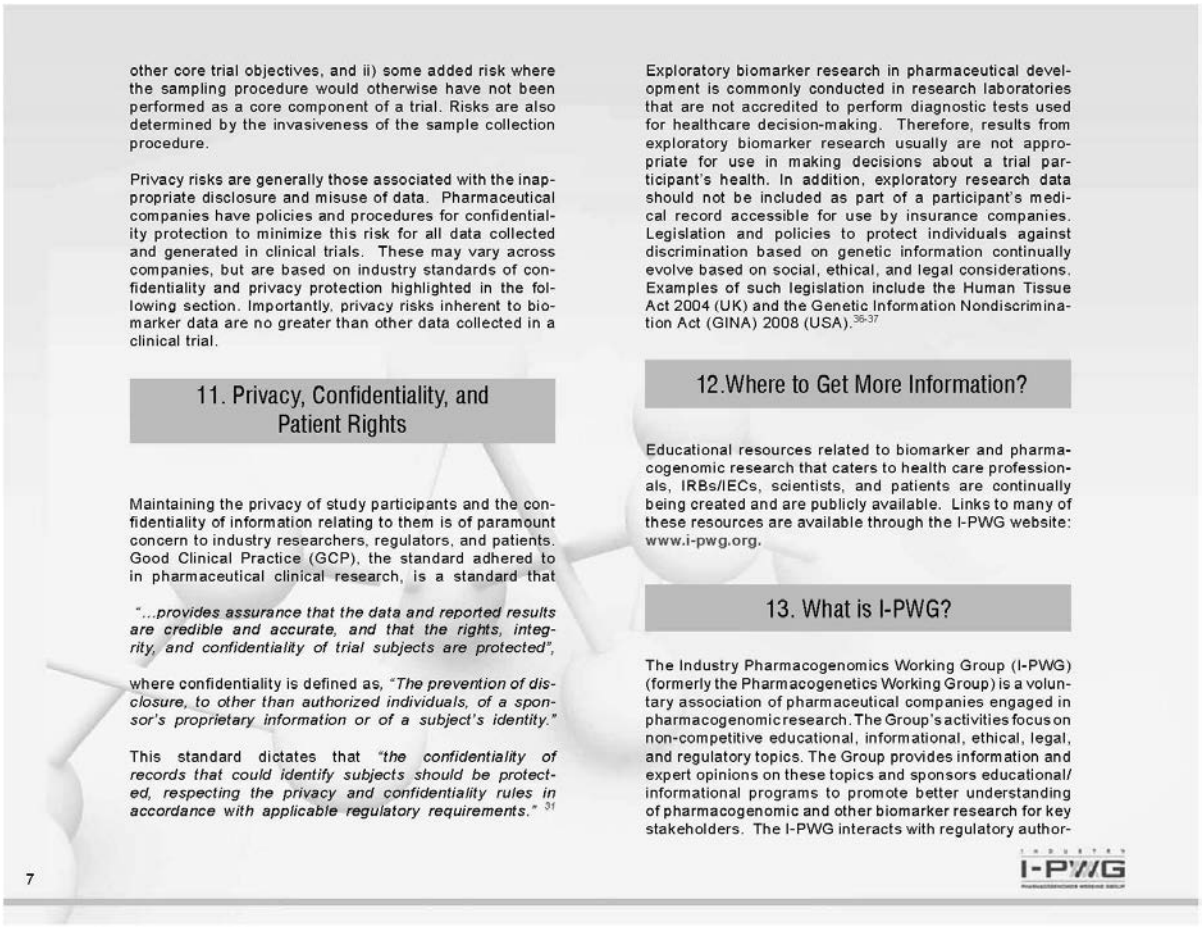

other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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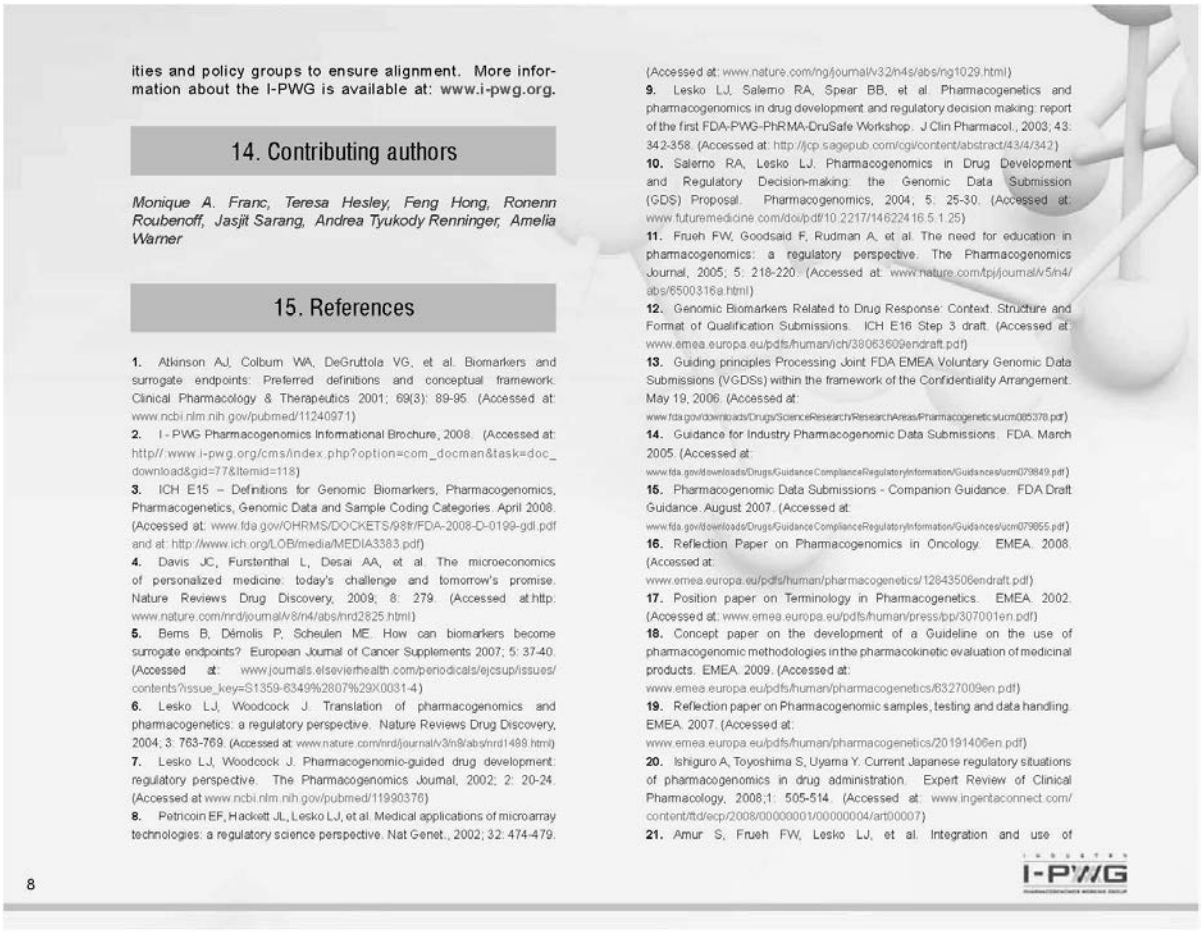

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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