Official Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study To Evaluate The Efficacy And Safety Of Ertugliflozin In Asian Subjects With Type 2 Diabetes Mellitus And Inadequate Glycemic Control On Metformin Monotherapy
NCT number:	NCT02630706
Document Date:	09 March 2014

CLINICAL PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 26-WEEK MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ERTUGLIFLOZIN IN ASIAN SUBJECTS WITH TYPE 2 DIABETES MELLITUS AND INADEQUATE GLYCEMIC CONTROL ON METFORMIN MONOTHERAPY

Compound:	MK-8835/PF-04971729
Compound Name:	Ertugliflozin
United States (US) Investigational New Drug (IND) Number:	Not Applicable
European Clinical Trial Database (EudraCT) Number:	Not Applicable
Protocol Number:	MK-8835-012-00 (Merck Protocol Number) B1521045 (Pfizer Protocol Number)
Phase:	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
Original protocol	09 March 2014	Not Applicable (N/A)

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 (SGLT1) and several other glucose transporters (GLUT1-4). Ertugliflozin inhibits renal glucose reabsorption resulting in urinary glucose excretion and thereby reducing plasma glucose and 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.

The purpose of this trial is to evaluate the efficacy and safety of the addition of ertugliflozin to the treatment regimen of Asian subjects with T2DM who have inadequate glycemic control on metformin monotherapy. The results of this study are intended to support the registration of ertugliflozin in China.

Objectives and Hypotheses:

The objectives listed below will be assessed in the overall study population and also in the China subpopulation (ie, subjects enrolled from China) in parallel. All hypotheses will be tested in the overall population; the primary hypotheses and secondary hypotheses 1-4 will also be tested in the China subpopulation (see Statistical Section 9.2.1 and 9.2.2).

In subjects with T2DM and inadequate glycemic control on metformin monotherapy, the following are primary objectives and hypotheses of the trial, after 26 weeks:

1. **Objective**: To assess the effect on HbA1c of 15 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in HbA1c for 15 mg ertugliflozin is greater than that for placebo.

2. **Objective**: To assess the effect on HbA1c of 5 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in HbA1c for 5 mg ertugliflozin is greater than that for placebo.

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

The secondary objectives and hypotheses of the trial are, after 26 weeks:

1. **Objective**: To assess the effect on fasting plasma glucose (FPG) of 15 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in FPG for 15 mg ertugliflozin is greater than that for placebo.

2. **Objective**: To assess the effect on FPG of 5 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in FPG for 5 mg ertugliflozin is greater than that for placebo.

3. **Objective**: To assess the effect on body weight of 15 mg ertugliflozin relative to placebo.

   Hypothesis: Ertugliflozin 15 mg reduces body weight relative to placebo.

4. **Objective**: To assess the effect on body weight of 5 mg ertugliflozin relative to placebo.

   Hypothesis: Ertugliflozin 5 mg reduces body weight relative to placebo.

5. **Objective**: To assess the proportion of subjects with an HbA1c <7.0% (53 mmol/mol) treated with 15 mg ertugliflozin relative to placebo.

   Hypothesis: The proportion of subjects with an HbA1c <7.0% (53 mmol/mol) treated with 15 mg ertugliflozin is greater than that for placebo.

6. **Objective**: To assess the proportion of subjects with an HbA1c <7.0% (53 mmol/mol) treated with 5 mg ertugliflozin relative to placebo.

   Hypothesis: The proportion of subjects with an HbA1c <7.0% (53 mmol/mol) treated with 5 mg ertugliflozin is greater than that for placebo.

7. **Objective**: To assess the effect on systolic blood pressure of 15 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in systolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

8. **Objective**: To assess the effect on systolic blood pressure of 5 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in systolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

9. **Objective**: To assess the effect on diastolic blood pressure of 15 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in diastolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

10. **Objective**: To assess the effect on diastolic blood pressure of 5 mg ertugliflozin relative to placebo.

    Hypothesis: The mean reduction from baseline in diastolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

11. **Objective:** To assess the proportion of subjects with an HbA1c <6.5% treated with ertugliflozin (for each dose) relative to placebo.

12. **Objective:** To assess the proportion of subjects requiring glycemic rescue therapy, and the time to initiation of glycemic rescue therapy with ertugliflozin (for each dose) relative to placebo.

13. **Objective:** To descriptively summarize pharmacokinetics of ertugliflozin and provide population PK [(pharmacokinetic(s)] analysis in this study.

Study Population:

Asian men and women, ≥18 years of age with T2DM, diagnosed in accordance with American Diabetes Association (ADA) guidelines, and inadequate glycemic control [HbA1c 7.0-10.5% (53-91 mmol/mol), inclusive] on metformin monotherapy at a stable dose of ≥1500 mg/day, for ≥ 8 weeks. In a country where the minimum age for consent and enrollment is ≥ 21 years of age, this age criterion should be followed.

Study Design:

This trial is a Phase 3 multi-center, randomized, parallel-group study with a 26-week, double-blind, placebo-controlled treatment period followed by a 2-week phone follow-up after the last dose of investigational product in Asian subjects with T2DM and inadequate glycemic control on metformin monotherapy.

The trial includes a fixed, 2-week single-blind placebo run-in from Screening Visit 3 (S3) to Day 1/Visit 4 which has the explicit purpose of familiarizing the subjects with the study treatment regimen and excluding subjects who are not compliant with the blinded placebo prior to randomization.

The trial is designed to accommodate subjects taking a variety of baseline diabetes therapy regimens at the Screening visit by incorporating a period of metformin titration and dose stabilization, and wash-off of another allowable anti-hyperglycemic agent (AHA) if necessary, prior to placebo run-in. Subjects will be eligible to screen for this trial if they are receiving one of the following diabetes therapy regimens at the time of Screening Visit 1 (S1):

- Metformin monotherapy;

- Combination therapy with metformin and **one** of the following allowable oral AHAs: sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, meglitinide, or alpha-glucosidase inhibitor.

Subjects receiving metformin in combination with another allowable AHA (as listed above) must discontinue the non-metformin AHA beginning at the Screening Visit 2 (S2) and remain off the non-metformin AHA for the duration of this trial, while they are receiving investigational product.

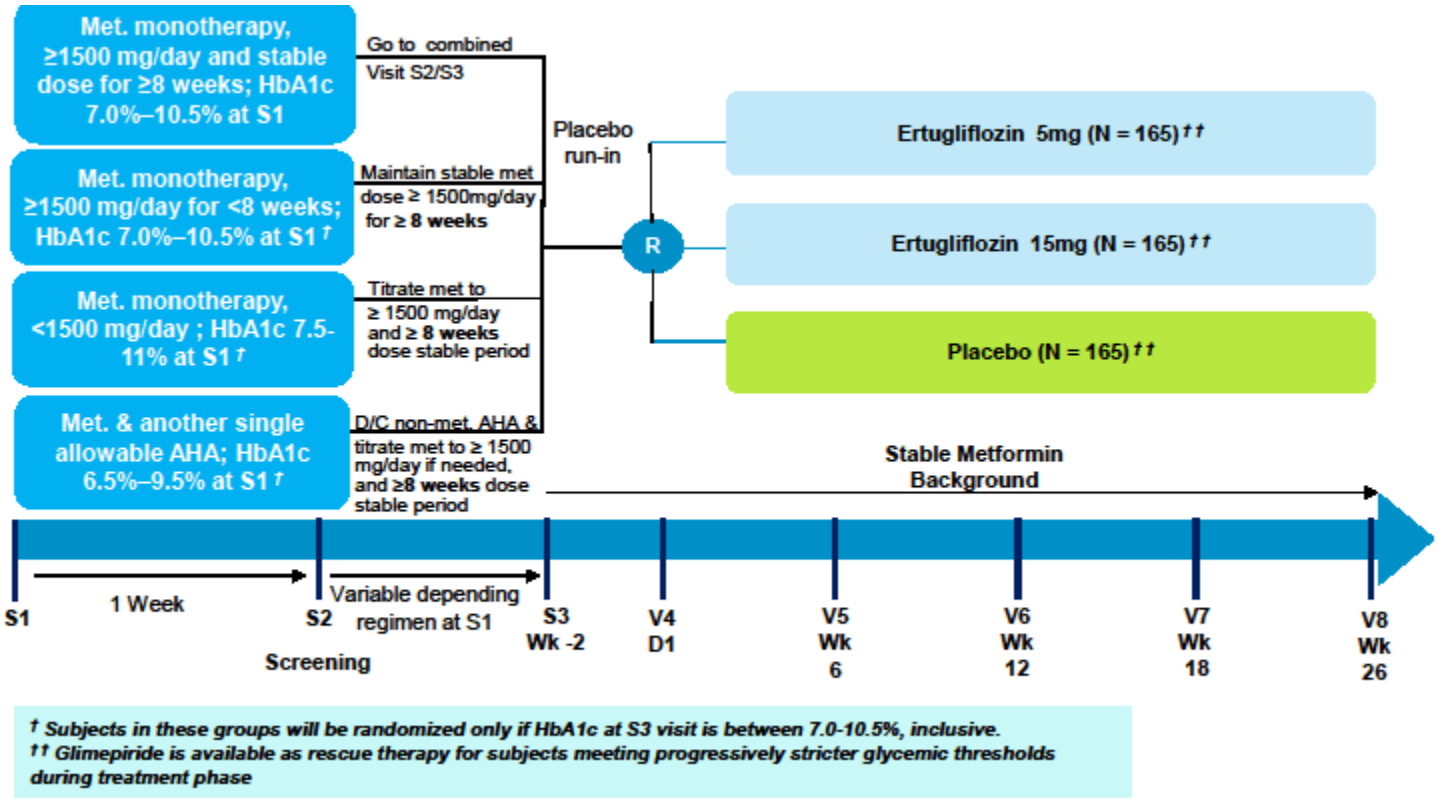
The following table provides information on the inclusion HbA1c levels at S1 based upon the background diabetes therapy. In addition, the table includes the subsequent actions to be taken based on the background diabetes regimen.

Table 1. Background Diabetes Therapy at Screening Visit 1 (S1), HbA1c Initial Inclusion and Appropriate Changes in Background Diabetes Therapy

Diabetes Therapy at S1	HbA1c Inclusion Criterion at S1	Change in Background Diabetes Therapy and Duration of Metformin Monotherapy Dose-Stable Period Prior to Placebo Run-in S3
Metformin monotherapy, ≥1500 mg/day, and stable dose for ≥8 weeks	7.0%–10.5% (53-91 mmol/mol), inclusive	None. Subjects proceed directly to a combined Screening Visit 2 and 3 (S2/S3).
Metformin monotherapy, ≥1500 mg/day for <8 weeks	7.0%–10.5% (53-91 mmol/mol), inclusive	Maintain metformin dose ≥1500 mg/day so subject has ≥8 weeks on stable dose.
Metformin monotherapy, <1500 mg/day	7.5%–11.0% (58-97 mmol/mol), inclusive	Titrate metformin dose to ≥1500 mg/day.** The dose stable period must be ≥8 weeks.
Metformin + another single allowable AHA*	6.5%–9.5% (48-80 mmol/mol), inclusive	Discontinue the non-metformin AHA. Titrate metformin dose to ≥1500 mg/day** (if needed). The dose stable period for metformin monotherapy must be ≥8 weeks.

HbA1c = Glycosylated hemoglobin; AHA = Anti-hyperglycemic agent; S1 = Initial screening visit; S2/S3 = Combined Screening Visits 2 and 3.
*allowable AHA agents are sulfonylurea, DPP-4 inhibitor, meglitinide, or alpha-glucosidase inhibitor.
** metformin can be uptitrated over a period of up to 4 weeks.

The trial is designed with two phases:



Met=Metformin

1. **Screening phase including discontinuation of background diabetes therapy other than metformin (if applicable) and a single-blind placebo run-in period (Visits S1 up to V4)** - the length of this standardization period will vary depending on the diabetes therapy of subjects at S1 (metformin monotherapy ≥1500 mg/day for ≥8 weeks or for <8 weeks, metformin monotherapy <1500 mg/day or metformin + another single allowable AHA) as shown in Table 1.

2. **Treatment Phase: Randomized, double-blind, placebo-controlled treatment period (Visits V4 through V8) -** a 26-week treatment period for assessment of primary efficacy and safety endpoints along with secondary efficacy endpoints. At entry into the double-blind treatment phase, subjects will be randomized to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo, while maintaining metformin at a stable dose (≥1500 mg/day). Glycemic rescue therapy with open-label glimepiride will be initiated in subjects with glucose values exceeding protocol-specified values as provided in Section 5.6. Dosing and titration of open-label glimepiride rescue therapy will be at the Investigator's discretion. After initiation of rescue therapy, background metformin (same dose and regimen) and blinded investigational product will continue to be taken by the subject. Each randomized subject should have a follow-up phone call 14 days after the last dose of investigational product to assess for AE (adverse event)s, SAE (serious adverse event)s and collect information on clinical events per Section 7.6, if applicable.

The trial is designed to evaluate the efficacy, safety and tolerability of the 5 mg and 15 mg oral doses of ertugliflozin on glycemic control, body weight, and blood pressure following a 26-week dosing period in Asian adult subjects with T2DM and inadequate glycemic control on metformin monotherapy.

Approximately 495 Asian subjects will be randomized into three trial arms in a 1:1:1 ratio (165 subjects/arm for ertugliflozin 5 mg, 15 mg and placebo respectively).

Glycemic Rescue Therapy:

Subjects will be prescribed rescue therapy in the form of open-label glimepiride, if they meet specific glycemic criteria with glucose values exceeding protocol-specified values as provided in Section 5.6. Dosing and titration of open-label glimepiride rescue therapy will be at the Investigator's discretion.

Endpoints:

Primary Endpoint:

- Change in HbA1c from Baseline to Week 26.

Secondary Endpoints:

- Change in FPG from Baseline to Week 26.

- Change in body weight from Baseline to Week 26.

- Proportion of subjects with HbA1c of <7.0% (53 mmol/mol) at Week 26.
- Change in systolic blood pressure from Baseline to Week 26.
- Change in diastolic blood pressure from Baseline to Week 26.
- Proportion of subjects with HbA1c <6.5% (48 mmol/mol) at Week 26.
- Proportion of subjects requiring glycemic rescue therapy by Week 26.
- Time to glycemic rescue therapy.
- Endpoints related to pharmacokinetics of ertugliflozin.

Statistical Methods:

All efficacy and safety analyses will be performed for the overall study population, as well as for the China subpopulation using the analysis methods described in Sections 9.2 and 9.3.

Sample Size: The sample size determination is based on the primary endpoint, reduction in HbA1c from baseline to Week 26, within the subjects enrolled from China. Assuming a standard deviation (SD) of 1.0%, the sample size of 105 Chinese subjects per group (total of 315 Chinese subjects) provides approximately 95% power to detect a difference in HbA1c of 0.5% between each ertugliflozin dose and placebo (and approximately 90% power for detecting this difference for both doses vs. placebo) using a two-sided 0.05 alpha level test. To control the overall Type I error rate at 0.05 within each population (ie, within the overall study population and within the China subpopulation) a sequential testing approach will be used across the primary and secondary efficacy endpoints for which hypotheses will be tested, and for the two doses of ertugliflozin. Assuming a drop-out rate of 20% by Week 26 (ie, either subjects who discontinue from the study, discontinue administration of IP (Investigational Product), or subjects who take rescue medication and are censored), approximately 396 subjects from China (132 per group) will be randomized. Additionally, this study will have approximately 99 subjects from at least two other Asian countries. The total sample size for this study is approximately 495 randomized subjects.

Primary analysis population: The primary analysis population for all efficacy analyses will be the Full Analysis Set defined separately for each analysis endpoint as all randomized subjects who have received at least one dose of investigational product and have at least one measurement of the respective endpoint at any time during the trial, including baseline and post-baseline time points. The post glycemic rescue therapy data from subjects who receive rescue therapy will be censored from primary and secondary endpoint efficacy analyses.

Efficacy analyses:

Analysis of Primary Endpoint:

The primary endpoint of HbA1c will be analyzed by fitting a constrained longitudinal data analysis model with terms for country (China, Other), treatment, visit, treatment by visit interaction, AHA status at study entry (binary) and Baseline eGFR (estimated glomerular filtration rate). Least-squares means and 95% confidence intervals will be used to estimate the treatment effect (difference between ertugliflozin and placebo) at the primary time point of Week 26. The two-sided p-value will also be provided for testing the significance of the difference between treatment groups. 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 within each population (overall study population and China subpopulation). Within each of these two populations, 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. The model utilized for the China subpopulation will not include country as a term.

Analysis of Secondary Endpoints:

The proportion of subjects with an HbA1c <7.0% (53 mmol/mol) at Week 26 will be analyzed using a logistic regression model with terms for country (categorical), treatment (categorical), baseline HbA1c (continuous), AHA status at study entry (binary) and Baseline eGFR (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 FPG, body weight, systolic blood pressure and diastolic blood pressure will be analyzed separately by fitting constrained longitudinal data analysis models similar to that used for the primary endpoint.

For the overall study population, the secondary efficacy endpoints of FPG, proportion of subjects achieving an HbA1c <7.0% (53 mmol/mol), body weight, systolic blood pressure and diastolic blood pressure will be tested for each ertugliflozin dose versus placebo using a multiple testing procedure that strongly controls the overall Type I error rate at 0.05. For the China subpopulation, due to smaller sample size, which limits the power for other secondary endpoints, only FPG and body weight endpoints will be tested for each ertugliflozin dose versus placebo using a multiple testing procedure that strongly controls the Type I error rate at 0.05, within the China subpopulation (ie, first FPG will be tested, and if both ertugliflozin doses are significant ($p< 0.05$), then body weight will be tested for each dose sequentially). The 95% CI with nominal p values will be provided for other secondary endpoints in the China subpopulation.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol 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 Activity	S1	S2[a]	S3	V4	V5	V6	V7	V8		
Study Day or Week[b]	N/A	N/A	Day -14	Day 1[c]	Wk 6	Wk 12	Wk 18	Wk 26 or ET[d]	2 Wk f/u phone call[e]	Rescue Visit[f]
Recommended Visit Window				±5 days	±7 days	±7 days	±7 days	±7 days	±3 days	
Informed Consent	X									
Contact IVRS System	X		X	X	X	X	X	X		
Assess Eligibility	X	X	X	X						
Randomization				X						
Provide Subject with Study Contact Card	X									
Demography, Height (measured in duplicate), & Medical History including smoking status	X									
Complete Physical Examination			X							
Brief Physical Examination[g]								X		X
Body Weight (measured in duplicate)	X		X	X	X	X	X	X		X
Triplicate Sitting Blood Pressure/Pulse Rate[h]	X			X	X	X	X	X		X
Postural (orthostatic) Blood Pressure/Pulse Rate (measured in duplicate)[i]			X	X	X			X		X
12-Lead ECG[j]			X					X		

Protocol Activity	S1	S2[a]	S3	V4	V5	V6	V7	V8		
Study Day or Week[b]	**N/A**	**N/A**	**Day -14**	**Day 1[c]**	**Wk 6**	**Wk 12**	**Wk 18**	**Wk 26 or ET[d]**	**2 Wk f/u phone call[e]**	**Rescue Visit[f]**
Recommended Visit Window				**±5 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±3 days**	
Laboratory										
Fasting Safety Lab Tests (hematology)	X			X		X		X		X
Fasting Safety Lab Tests (chemistry)	X			X	X	X	X	X		X
Urinalysis[k, l]		X		X				X		X
Urinary Albumin/Creatinine Ratio[l]				X				X		
Fasting Fingerstick Glucose in Clinic		X	X	X[m]						
Fasting Triglycerides/TSH	X									
Lipid Panel[n]				X				X		X
Pregnancy Test (women of childbearing potential only)[o]	X		X	X	X	X	X	X		
HbA1c	X		X[p]	X	X	X	X	X[q]		X[q]
Fasting Plasma Glucose	X			X	X	X	X	X		X
PK Sample for ertugliflozin[r]					X	X	X	X		
Drug										
Dispense Single-Blind Placebo Run-in Investigational Product			X							
Dispense Double-Blind Investigational Product				X	X	X	X			
Witnessed dose of Investigational Product in Clinic			X	X		X	X			
Dispense glimepiride glycemic rescue medication as appropriate					X	X	X			X
Assess Compliance to Investigational Product				X	X	X	X	X		X
Prior/Concomitant medication review	X	X	X	X	X	X	X	X		X

Protocol Activity	S1	S2[a]	S3	V4	V5	V6	V7	V8		
Study Day or Week[b]	N/A	N/A	Day -14	Day 1[c]	Wk 6	Wk 12	Wk 18	Wk 26 or ET[d]	2 Wk f/u phone call[e]	Rescue Visit[f]
Recommended Visit Window				±5 days	±7 days	±7 days	±7 days	±7 days	±3 days	
Subject Education / Monitoring										
Diet and Exercise Counseling (S2)/Monitoring[s]		X	X	X	X	X	X	X		X
Distribute glucose meter (S2 only) and glucose meter supplies (other visits as designated)		X	X	X	X	X	X			X
Dispense Hypoglycemia Assessment and Self-Monitoring Blood Glucose logs and instruct on hypoglycemia (symptoms and management) and hyperglycemia symptoms[t]		X								
Review/dispense Hypoglycemia Assessment and Self-Monitoring Blood Glucose logs			X	X	X	X	X	X[u]		X
Adverse Event Monitoring[v]		X	X	X	X	X	X	X	X	X

a. A separate S2 visit is required for subjects taking metformin monotherapy for less than 8 weeks at the S1 visit and for those who require a change to their diabetes regimen at the S2 visit (including subjects who require discontinuation of their non-metformin AHA therapy at the S2 visit). These subjects must remain on a stable dose of metformin monotherapy ≥1500 mg/day for at least 8 weeks prior to repeating the HbA1c at S3 for determination of eligibility. Subjects whose HbA1c at S1 is ≥7.0 and ≤10.5% and are on a stable dose of metformin monotherapy ≥1500 mg/day for at least 8 weeks at S1, will have a combined S2/S3 visit.

b. Day 1 has a recommended visit window of ±5 days relative to S3 (or combined S2/S3 visit); Weeks 6, 12, 18, 26 have a recommended visit window of ±7 days relative to Day 1.

c. All Day 1 procedures to be completed prior to dosing.

d. ET = Early termination, subjects who discontinue taking investigational product prematurely should complete procedures for the ET visit and have a 2-week follow-up phone call from their last dose of investigational product. In addition, if subjects agree, they will also be contacted via telephone by the Investigator/qualified designee according to the same schedule as if the subjects were still taking investigational product to assess for SAEs and to collect information on clinical events per Section 7.6 if applicable. See Section 6.6 for additional details.

e. Each randomized subject should have a follow-up phone call 14 ±3 days after the last dose of investigational product to assess for SAEs and to collect information on clinical events per Section 7.6, if applicable.

f. Subjects who require glycemic rescue therapy per Section 5.6 must have glycemic rescue therapy initiated at either a scheduled or unscheduled visit, and not by a telephone call.

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

h. Sitting triplicate blood pressure and pulse rate should be collected, as instructed in Section 7.4.2.

i. Duplicate measurements of supine and standing blood pressure and pulse rate should be taken per Section 7.4.3.

j. ECGs scheduled in the trial are initially assessed at the investigative site for subject safety and then submitted to be read centrally. ECGs should be obtained prior to the nominal time assessment of blood pressure, and pulse rate as well as prior to blood collection.
k. Samples collected for urinalysis will be sent to the central laboratory for dipstick analysis (not including urinary glucose assessment) and microscopy if the laboratory performed dipstick is positive for blood, nitrites, leukocytes and/or protein.
l. Urine sample(s) for urinalysis and albumin:creatinine ratio should not be obtained if the subject is menstruating, has vigorously exercised within 24 hours or had fever or an active infection within 2 days of the visit. Under these circumstances, the subject should provide a urine sample for evaluation at an unscheduled visit.
m. If fasting fingerstick glucose (FFSG) <120 mg/dL (6.7 mmol/L) or >270 mg/dL (15.0 mmol/L) AND the investigator believes that the value is not consistent with the subject's current self-monitoring blood glucose (SMBG) values, the subject should not be excluded at this time. The subject should be rescheduled for Visit 4/Day 1 within 7 days. FFSG should be re-tested at rescheduled Visit 4 and only those whose re-test FFSG is eligible can proceed into the study. In such cases, the sites will need to repeat all Visit 4/Day 1 procedures (See Section 6.3.1).
n. Includes total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, non-HDL-C and triglycerides at all time points noted above.
o. Urine pregnancy tests will be performed for women of childbearing potential at all time points noted above, and if positive must be confirmed with a serum pregnancy test. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
p. Subjects taking metformin monotherapy for less than 8 weeks at S1 or who require a change to their diabetes regimen at the S2 visit to remain eligible to participate (including subjects discontinuing their non-metformin AHA therapy at S2) must have an HbA1c of 7.0-10.5% (53-91 mmol/mol) at S3 in order to be randomized.
q. HbA1c should not be obtained if ET or rescue visit occurs within 6 weeks of randomization.
r. PK samples are to be collected at approximately 24 hour following the prior day's dose and before administration of the current day's dose. In addition, PK samples will also be collected 1 hr post dose at Weeks 12 and 18 (with an allowable time window up to 3 hours post dose).
s. Subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at S2 only; at other visits subjects should be asked about their diet and exercise which may be done by other appropriate site personnel evaluating the subject.
t. Subjects should be educated on the symptoms of hyperglycemia (eg, polyuria, polydipsia) at S2.
u. At Week 26 visit, only need to collect and review Hypoglycemia Assessment and Self-Monitoring Blood Glucose logs, there is no dispensing of additional logs at this visit.
v. Assess AEs, SAEs, hypoglycemia assessment log as well as potential clinical events for adjudication (See Section 7.4.6, 7.6, 8 for additional detail).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
β-hCG	beta human chorionic gonadotropin
ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE	adverse event
AHA	anti-hyperglycemic agent
ALT	alanine transaminase
ANCOVA	analysis of covariance
ASaT	All Subjects as Treated
AST	aspartate transaminase
AUC	area under the concentration-time curve
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
CHF	Congestive heart failure
C_{max}	maximum observed measurable concentration
CRA	clinical research associate
CRF	case report form
CSA	clinical study agreement
CV	cardiovascular
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
ECI	event of clinical interest
ED_{50}	dose achieving 50% of maximum response
eGFR	estimated glomerular filtration rate
ER	Extended Release
ET	early termination of the study
FDA	Food and Drug Administration
FFSG	fasting fingerstick glucose

FPG	fasting plasma glucose
GCP	Good Clinical Practice
HA	hypoglycemia assessment
HbA1C	glycated/glycosylated hemoglobin
HDL-C	high density lipoprotein cholesterol
HR	heart rate
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IND	investigational new drug application
IP	Investigational Product
IR	Immediate Release
IRB	institutional review board
IUD	Intra-uterine device
IVRS	interactive voice response system
LDL-C	low density lipoprotein cholesterol
MACE	major adverse cardiovascular events
Met	metformin
MDRD	Modification of Diet in Renal Disease
N/A	Not applicable
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
PK	pharmacokinetic(s)
PR interval	time from the beginning of the P wave to the end of the QRS complex on electrocardiogram
QD	once daily
QRS	the deflections in an electrocardiographic tracing and represent ventricular activity of the heart
QT	time from the beginning of the QRS complex to the end of the T wave on electrocardiogram
QTcB	corrected QT interval Bazett's formula
QTcF	corrected QT interval Fridericia's formula
S1	Screening Visit 1

S2	Screening Visit 2
S3	Screening Visit 3
S2/S3	combined Screening Visits 2 and 3
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGLT1	Sodium Glucose co-Transporter 1
SGLT2	Sodium Glucose co-Transporter 2
SLC5A	Sodium Glucose co-Transporter gene family
SMBG	Self-monitoring blood glucose
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reactions
T2DM	type 2 diabetes mellitus
TIA	Transient ischemic attack
TSH	thyroid-stimulating hormone
UGE	urinary glucose excretion
US	United States
UTI	urinary tract infections

1. INTRODUCTION

1.1. Indication

Use in patients with type 2 diabetes mellitus (T2DM) to improve glycemic control with once daily dosing with the Sodium Glucose co-Transporter 2 (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 the prevalence of diabetes is projected to reach more than 550 million by the year 2030.[1] In China, the population with T2DM was reported as 90 million in the year 2011with a prevalence of 9.3%. It is estimated that by 2030, the prevalence of T2DM in China will increase to 12.1% and the total T2DM population in China will be around 129.7 million.[2,3] T2DM accounts for approximately 90-95% of all cases of diabetes. Approximately 85% of patients with T2DM are obese or overweight, a key factor underlying the development and maintenance of insulin resistance.[4,5] Individuals with T2DM have an increased risk of developing both microvascular and macrovascular disease-associated complications, including nephropathy, neuropathy, retinopathy, and cardiovascular disease, and are 2 to 4 times more likely to die from cardiovascular disease than adults who do not have diabetes.[6]

The sodium glucose co-transporter family (SLC5A) consists of 12 known members, including 6 gene products named SGLTs.[7] 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.[8,9,10]

Ertugliflozin (MK-8835/PF-04971729) is a potent inhibitor of the Sodium Glucose co-transporter type 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 HbA1c in subjects with T2DM. Ertugliflozin is being developed as an adjunct to diet and exercise to improve glycemic control in patients with T2DM.

The purpose of this trial is to evaluate the efficacy and safety of the addition of ertugliflozin to the treatment of Asian subjects with T2DM who have inadequate glycemic control on metformin monotherapy.

Metformin is the standard and preferred first line pharmacological agent for T2DM. However, due to the progressive nature of T2DM, many subjects may have poor glycemic control despite metformin monotherapy. Since ertugliflozin improves glycemic control via a mechanism independent of insulin, it could potentially represent a valuable therapy across the typical disease progression of T2DM, including individuals with inadequate glycemic control on metformin monotherapy.

1.3. 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 who were receiving metformin monotherapy, the following placebo-adjusted mean (80% confidence interval [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 placebo-adjusted mean reductions in diastolic blood pressure for the 5 mg, 10 mg and 25 mg doses were: -2.03 (-3.68 to -0.37), -4.12 (-5.81 to -2.42) and -2.40 (-4.08 to -0.73) respectively.

1.4. Safety Information for Ertugliflozin and Other SGLT2 Inhibitors

Several SGLT2 inhibitors are in clinical development and as of January 2014, two SGLT2 inhibitors (dapagliflozin and canagliflozin) are approved in the U.S. and the European Union. Based on available clinical trial data with dapagliflozin and canagliflozin, several potential risks from SGLT2 inhibition have been identified. In clinical trials, the rate of genital fungal infections in males and females has consistently been higher in subjects receiving SGLT2 inhibitors as compared to placebo or other diabetes medications. Therefore, the increased risk of genital fungal infections can be considered a class effect of SGLT2 inhibitors. Glucosuria can potentially result in increased risk of urinary tract infection (UTI). In some clinical trials with SGLT2 inhibitors, the reported rate of UTI was slightly higher in subjects treated with an SGLT2 inhibitor compared to those receiving placebo.

SGLT2 inhibition leads to an increase in urinary excretion of glucose and sodium, a diuretic effect and a decrease in blood pressure similar to that reported with other agents with a diuretic action. In clinical trials with other SGLT2 inhibitors, this diuretic effect led to a higher frequency of adverse events such as pollakiuria, thirst and polyuria, but these events were typically of mild severity and usually did not lead to discontinuation. However, certain populations of subjects (eg, elderly or renal insufficient) may be at risk for hypovolemia-related adverse events from this mechanism. As SGLT2 inhibition can lead to volume depletion, there is also a potential concern for decreased estimated glomerular filtration rate (eGFR) on a hemodynamic basis. In subjects with moderate renal impairment, there was a slightly higher incidence of renal-related adverse events reported in subjects

receiving SGLT2 inhibitors than controls in clinical trials with other SGLT2 inhibitors. Small initial decreases in the estimated glomerular filtration rate (eGFR) were seen, which returned toward baseline levels over time with continued treatment and/or upon discontinuation of therapy, consistent with a reduction in plasma volume. The reversibility with continued treatment or with discontinuation of treatment is consistent with a hemodynamic (plasma volume) mechanism.

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. At the completion of Phase 2, a total of 479 subjects had been exposed to ertugliflozin in six completed Phase 1 and two completed Phase 2 studies. Oral doses of ertugliflozin as high as 300 mg (single dose), 100 mg once daily (up to 14 days), and 25 mg once daily (up to 12 weeks) were well tolerated with a safety profile supporting continued development.

As of December 2013, there were no deaths, and a total of 11 Serious Adverse Events (SAEs) were reported in 9 subjects. Across the program, a total of 10 subjects (1.5%) were withdrawn due to adverse events (AEs). The most frequent AEs reported with ertugliflozin use in the Phase 1 studies have been headache, constipation, diarrhea and nausea. In the two Phase 2 studies, upper respiratory, urinary tract and genital fungal infections, diarrhea, arthralgia and headache were most frequently reported. The incidences of these AEs however, were low. UTI was reported at a frequency of 3.3% for all ertugliflozin doses combined, versus 5.4% for placebo. The frequency of genital fungal infection was noted to be numerically higher in males and females receiving ertugliflozin treatment compared to placebo, and currently this AE is the only event considered to be an adverse drug reaction (ADR) for ertugliflozin. Overall, there was no clear dose-related increase in frequency of AEs with increasing dose of ertugliflozin.

In the Phase 2 study B1521004, a mild diuretic effect was observed with ertugliflozin (ie, increase in 24-hour urinary volume) though there was a lack of a dose-response relationship across the doses of ertugliflozin. In susceptible individuals, this diuretic effect from ertugliflozin could lead to volume depletion and related adverse events such as hypotension or dizziness, and these events will be monitored in the Phase 3 studies.

In Phase 2, there were small increases observed in hemoglobin and hematocrit, suggestive of hemoconcentration, and a small increase in blood-urea-nitrogen (BUN) but no change in serum creatinine, at Week 12 relative to Baseline. Given the small magnitude of the increases in BUN, and hemoglobin/hematocrit, these changes are unlikely to have clinical consequence.

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

Phase 3 clinical trial data from another SGLT2 inhibitor, dapagliflozin, revealed a numerical imbalance in the rates of breast and bladder cancer in dapagliflozin-treated subjects compared to control.[9] The causal relationship to dapagliflozin for this finding is uncertain given the small number of events and the absence of any preclinical signal (ie, no reported increase in either tumor in carcinogenicity studies) with dapagliflozin. Moreover, in the larger clinical program of another SGLT2 inhibitor, canagliflozin, no cancer imbalance, including in breast or bladder cancer events, was reported. Because thorough evaluation of malignancies is important in the development program of all investigational medications, detailed information will be collected for subjects who develop a malignancy. This information could include but is not limited to relevant medical history, biopsy, or operative reports, etc.

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

1.5. Rationale for Study and Design

SGLT2 inhibitors lower blood glucose in an insulin-independent manner. Consequently, glucose lowering should be observed across the typical continuum of T2DM progression, ranging from subjects treated with diet and exercise alone to subjects receiving insulin.

This trial will assess the efficacy and safety of ertugliflozin added to the regimen of Asian subjects who have inadequate glycemic control on metformin monotherapy at or near maximally effective doses (ie, ≥1500 mg/day). Subjects already on metformin monotherapy at protocol-specified doses (≥1500 mg/day) for at least 8 weeks at S1 and who meet other enrollment criteria will go directly from S1 to S2/3 to enter the 2-week single-blind placebo run-in period.

In addition to subjects with inadequate control on metformin monotherapy at ≥1500 mg/day for ≥8 weeks, a broader range of subjects will be screened for the study. This includes subjects who have been on a stable dose of metformin ≥1500 mg/day for <8 weeks, or metformin monotherapy at a dose <1500 mg/day as well as subjects on metformin in combination with another allowable single AHA agent. Subjects not yet on a stable dose of metformin monotherapy ≥1500 mg/day for at least 8 weeks will enter a dose stable period at S2, so that they have received at least 8 weeks of a stable dose of metformin monotherapy prior to S3, where they will enter a 2 week single-blind placebo run-in period. Subjects receiving metformin and another allowable single AHA will discontinue the non-metformin AHA at S2 and enter a metformin monotherapy period (uptitrate metformin dose to ≥1500 mg/day if applicable) and reach a stable dose of ≥1500 mg/day for at least 8 weeks prior to S3. With the exception of subjects who at S1 are already receiving metformin monotherapy ≥1500 mg/day for at least 8 weeks, subjects on other allowable diabetes medications at S1 will have HbA1c measured again at S3 to determine if they qualify for enrollment.

The population to be enrolled in this study represents subjects appropriate to assess the primary and secondary objectives in the study.

1.5.1. Rationale for Dose Selection of Ertugliflozin

The proposed ertugliflozin doses to be 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 FPG) from study B1521006 as well as 24-hour urinary glucose excretion (mechanism biomarker) in T2DM subjects from study B1521004. For these end points, the 5 mg and 15 mg doses consistently elicit a response that is >80% and >90% of the maximum response, respectively (Table 2).

Table 2. Estimated Percent Maximum Response for Various Endpoints

Ertugliflozin Dose	UGE – T2DM (ED_{50}=0.78 mg)	HbA1C (ED_{50}=1 mg)	FPG (ED_{50}=1.1 mg)
5 mg	87%	83%	82%
15 mg	95%	94%	93%

ED_{50}= dose achieving 50% of maximum response
UGE= urinary glucose excretion

In addition, the dose-response modeling of 24-hour urinary glucose excretion (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 $(AUC)_{(0-24)}$] lower than exposure at the no observed adverse effect level (NOAEL) in the 6-month toxicology study in the most sensitive species (rat). Data from study B1521009 provide support for study of 5 mg and 15 mg doses of ertugliflozin in Asian subjects in study B1521045. In study B1521009, the pharmacokinetics and pharmacodynamics of ertugliflozin were studied in healthy Japanese subjects following administration of single (1, 5 and 25 mg) and multiple (25 mg once daily for 7 days) oral doses of ertugliflozin. Western healthy subjects were included in the single dose portion of this study for comparison of pharmacokinetics and pharmacodynamics between healthy Japanese and Western subjects. Results from this study suggest that clinically meaningful differences between Asian and Western subjects in ertugliflozin pharmacokinetics and pharmacodynamics are not likely to exist. 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.

2. STUDY OBJECTIVES, HYPOTHESES AND ENDPOINTS

2.1. Objectives and Hypotheses

The objectives listed below will be assessed in the overall study population and also in the China subpopulation (subjects enrolled from China) in parallel. All hypotheses will be tested in the overall population; the primary hypotheses and secondary hypotheses 1-4 will also be tested in the China subpopulation (see Statistical Sections 9.2.1 and 9.2.2).

In subjects with T2DM and inadequate glycemic control on metformin monotherapy, the following are primary objectives and hypotheses of the trial, after 26 weeks:

1. **Objective**: To assess the effect on HbA1c of 15 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in HbA1c for 15 mg ertugliflozin is greater than that for placebo.

2. **Objective**: To assess the effect on HbA1c of 5 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in HbA1c for 5 mg ertugliflozin is greater than that for placebo.

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

The secondary objectives and hypotheses of the trial are, after 26 weeks:

1. **Objective**: To assess the effect on fasting plasma glucose (FPG) of 15 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in FPG for 15 mg ertugliflozin is greater than that for placebo.

2. **Objective**: To assess the effect on FPG of 5 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in FPG for 5 mg ertugliflozin is greater than that for placebo.

3. **Objective**: To assess the effect on body weight of 15 mg ertugliflozin relative to placebo.

   Hypothesis: Ertugliflozin 15 mg reduces body weight relative to placebo.

4. **Objective**: To assess the effect on body weight of 5 mg ertugliflozin relative to placebo.

   Hypothesis: Ertugliflozin 5 mg reduces body weight relative to placebo.

5. **Objective**: To assess the proportion of subjects with an HbA1c <7.0% (53 mmol/mol) treated with 15 mg ertugliflozin relative to placebo.

Hypothesis: The proportion of subjects with an HbA1c <7.0% (53 mmol/mol) treated with 15 mg ertugliflozin is greater than that for placebo.

6. **Objective**: To assess the proportion of subjects with an HbA1c <7.0% (53 mmol/mol) treated with 5 mg ertugliflozin relative to placebo.

   Hypothesis: The proportion of subjects with an HbA1c <7.0% (53 mmol/mol) treated with 5 mg ertugliflozin is greater than that for placebo.

7. **Objective**: To assess the effect on systolic blood pressure of 15 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in systolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

8. **Objective**: To assess the effect on systolic blood pressure of 5 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in systolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

9. **Objective**: To assess the effect on diastolic blood pressure of 15 mg ertugliflozin relative to placebo.

   Hypothesis: The mean reduction from baseline in diastolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

10. **Objective**: To assess the effect on diastolic blood pressure of 5 mg ertugliflozin relative to placebo.

    Hypothesis: The mean reduction from baseline in diastolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

11. **Objective:** To assess the proportion of subjects with an HbA1c <6.5% treated with ertugliflozin (for each dose) relative to placebo.

12. **Objective:** To assess the proportion of subjects requiring glycemic rescue therapy, and the time to initiation of glycemic rescue therapy with ertugliflozin (for each dose) relative to placebo.

13. **Objective:** To descriptively summarize pharmacokinetics of ertugliflozin and provide population PK analysis in this study.

2.2. Endpoints

2.2.1. Primary Endpoint

- Change in HbA1c from Baseline to Week 26.

2.2.2. Secondary Endpoints

- Change in FPG from Baseline to Week 26.
- Change in body weight from Baseline to Week 26.
- Proportion of subjects with HbA1c of <7.0% (53 mmol/mol) at Week 26.
- Change in systolic blood pressure from Baseline to Week 26.
- Change in diastolic blood pressure from Baseline to Week 26.
- Proportion of subjects with HbA1c <6.5% (48 mmol/mol) at Week 26.
- Proportion of subjects requiring glycemic rescue therapy by Week 26.
- Time to glycemic rescue therapy.
- Endpoints related to pharmacokinetics of ertugliflozin.

This trial will utilize an external Data Monitoring Committee (E-DMC) to periodically review safety data.

3. STUDY DESIGN

This trial is a Phase 3 multi-center, randomized, parallel-group study with a 26-week, double-blind, placebo-controlled treatment period followed by a 2-week phone follow-up after the last dose of investigational product in Asian subjects with T2DM and inadequate glycemic control on metformin monotherapy.

The trial includes a fixed, 2-week placebo run-in from S3 to Day 1/Visit 4 which has the explicit purpose of familiarizing the subjects with the study treatment regimen and excluding subjects who are not compliant with the blinded placebo prior to randomization.

The trial is designed to accommodate subjects taking a variety of baseline diabetes therapy regimens at S1 by incorporating a period of metformin dose titration and stabilization, and wash off of another allowable anti-hyperglycemic agent (AHA) if necessary, prior to placebo run-in. Subjects will be eligible to screen for this trial if they are receiving one of the following diabetes therapy regimens at the time of S1:

- Metformin monotherapy;
- Combination therapy with metformin and **one** of the following allowable oral AHAs: sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, meglitinide, or alpha-glucosidase inhibitor.

Subjects receiving metformin in combination with another allowable AHA (as listed above) must discontinue the non-metformin AHA beginning at S2 and remain off the non-metformin AHA for the duration of this trial, while they are receiving investigational product.

The following table provides information on the inclusion HbA1c levels at S1 based upon the background diabetes therapy. In addition, the table includes the subsequent actions to be taken based on the background diabetes regimen.

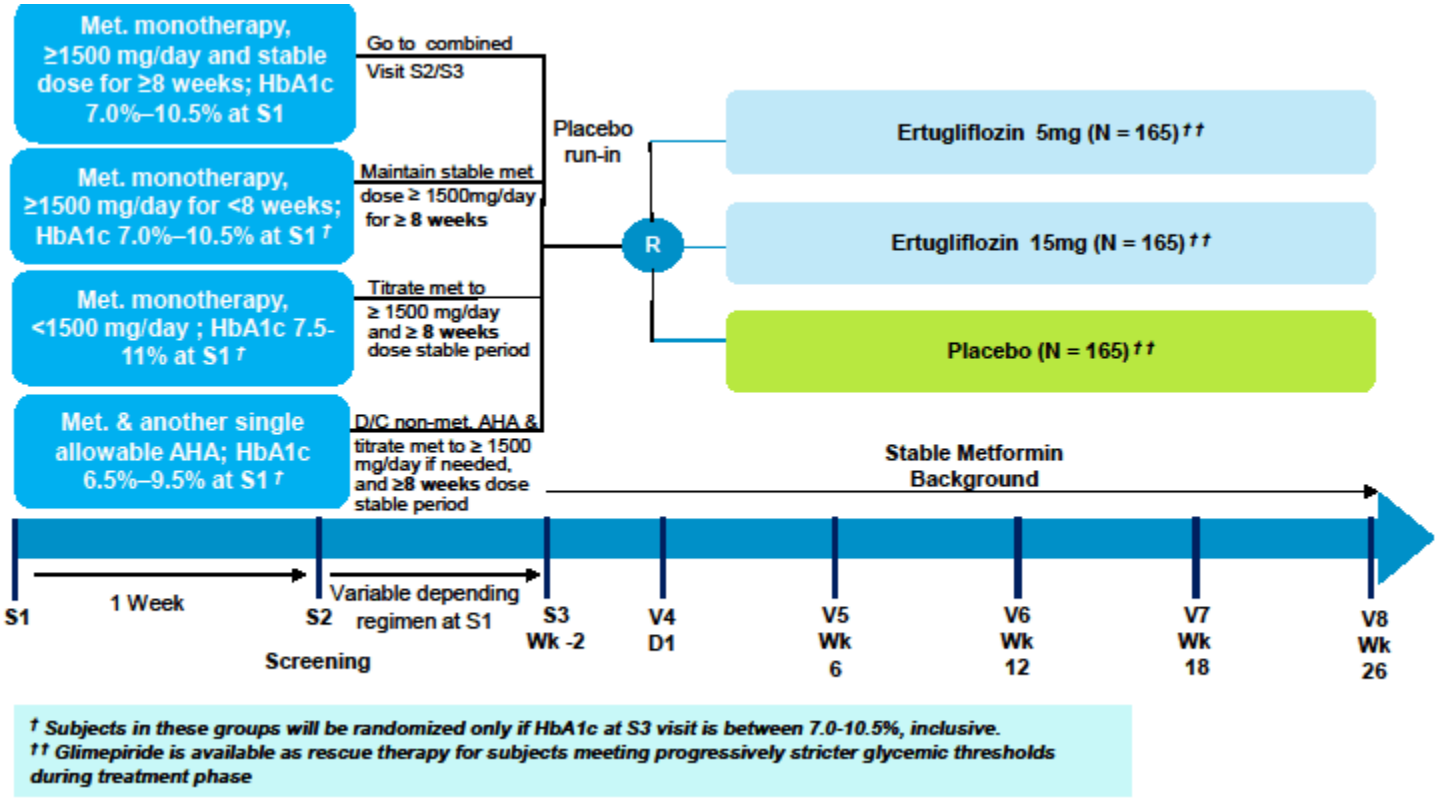
Table 3. Background Diabetes Therapy at Screening Visit 1 (S1), HbA1c Initial Inclusion and Appropriate Changes in Background Diabetes Therapy

Diabetes Therapy at S1	HbA1c Inclusion Criterion at S1	Change in Background Diabetes Therapy and Duration of Metformin Monotherapy Dose-Stable Period Prior to Placebo Run-in S3
Metformin monotherapy, ≥1500 mg/day, and stable dose for ≥8 weeks	7.0%–10.5% (53-91 mmol/mol), inclusive	None. Subjects proceed directly to S2/S3.
Metformin monotherapy, ≥1500 mg/day for <8 weeks	7.0%–10.5% (53-91 mmol/mol), inclusive	Maintain metformin dose ≥1500 mg/day so subject has ≥8 weeks on stable dose.
Metformin monotherapy, <1500 mg/day	7.5%–11.0% (58-97 mmol/mol), inclusive	Titrate metformin dose to ≥1500 mg/day.** The dose stable period must be ≥8 weeks.
Metformin + another single allowable AHA*	6.5%–9.5% (48-80 mmol/mol), inclusive	Discontinue the non-metformin AHA. Titrate metformin dose to ≥1500 mg/day** (if needed). The dose stable period for metformin monotherapy must be ≥8 weeks.

HbA1c = Glycosylated hemoglobin; AHA = Anti-hyperglycemic agent; S1 = Initial screening visit; S2/S3 = Combined Screening Visits 2 and 3.
*allowable AHA agents are sulfonylurea, DPP-4 inhibitor, meglitinide, or alpha-glucosidase inhibitor.
** metformin can be uptitrated over a period of up to 4 weeks.

Figure 1 summarizes the overall trial scheme.

Figure 1. Trial Scheme



Met=Metformin

The trial is designed with two phases:

1. **Screening phase including discontinuation of background diabetes therapy other than metformin (if applicable) and a single-blind placebo run-in period (Visits S1 up to V4)** - the length of this standardization period will vary depending on the diabetes therapy of subjects at S1 (metformin monotherapy ≥1500 mg/day for ≥8 weeks or for <8 weeks, metformin monotherapy <1500 mg/day or metformin + another single allowable AHA) as shown in Table 3.

2. **Treatment Phase: Randomized, double-blind, placebo-controlled treatment period (Visits V4 through V8) -** a 26-week treatment period for assessment of primary efficacy and safety endpoints along with secondary efficacy endpoints. At entry into double-blind treatment phase, subjects will be randomized to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo, while maintaining metformin at a stable dose (the metformin dose at which the subject entered the metformin dose-stable run-in period). Glycemic rescue therapy with open-label glimepiride will be initiated in subjects with glucose values exceeding protocol-specified values as provided in Section 5.6. Dosing and titration of open-label glimepiride rescue therapy will be at the Investigator's discretion. After initiation of rescue therapy, background metformin (same dose and regimen) and blinded investigational product will continue to be taken by the subject. 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 per Section 7.6, if applicable.

The trial is designed to evaluate the efficacy, safety and tolerability of the 5 mg and 15 mg oral doses of ertugliflozin on glycemic control, body weight, and blood pressure following a 26-week dosing period in Asian adult subjects with T2DM and inadequate glycemic control on metformin monotherapy.

Approximately 495 Asian subjects including approximately 396 subjects from China, 99 subjects from at least two other Asian countries will be randomized (165 subjects to ertugliflozin 5mg, 15mg and placebo respectively). This sample size accounts for an approximate 20% premature withdrawal rate (ie, either subjects who discontinue from the study or IP, or subjects who take rescue medication and are censored) and ensures an adequate number of subjects have evaluable data for the primary endpoint of HbA1c at Week 26.

4. SUBJECT SELECTION

This trial can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol 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 study team before subjects are included in the trial.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the trial:

1. Asian subject ≥18 years of age at the time of the initial Screening Visit (S1) with a diagnosis of T2DM in accordance with American Diabetes Association (ADA) guidelines.[19] In a country where the minimum age for consent and enrollment is ≥21 years of age, this age criterion should be followed.

2. Subject receiving one of the following diabetes therapy regimens at the time of S1 and with an HbA1c within the following range:

Diabetes Medication at S1	HbA1c Inclusion Criterion at S1
Metformin monotherapy, ≥1500 mg/day	7.0-10.5% (53-91 mmol/mol), inclusive
Metformin monotherapy, <1500 mg/day	7.5-11.0% (58-97 mmol/mol), inclusive
Dual combination therapy with metformin + sulfonylurea, DPP-4 inhibitor, meglitinide, or alpha-glucosidase inhibitor	6.5-9.5% (48-80 mmol/mol), inclusive

3. Subjects taking metformin monotherapy for less than 8 weeks at S1 or who require a change to their diabetes regimen at the S2 visit to remain eligible to participate (including subjects discontinuing non-metformin AHA therapy at S2 or requiring metformin dose titration) must have an HbA1c of 7.0-10.5% (53-91 mmol/mol) at S3 after at least 8 weeks on a stable dose regimen of metformin monotherapy ≥1500 mg/day. Subjects receiving a stable dose of metformin monotherapy ≥1500 mg/day for at least 8 weeks prior to S1 and meeting eligibility, do not need to have an HbA1c performed at S3.

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

5. Evidence of a personally signed and dated informed consent document indicating that the subject (or legal representative) has been informed of all pertinent aspects of the trial.

6. Subjects who, in the opinion of the Investigator, are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

7. Subject meets one of the following criteria:

    a. Is a male.

    b. Is a female not of reproductive potential defined as one who (See Sections 4.5.1 and 4.5.2 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 S1.

c. Is a female of reproductive potential and:

1. Agrees to remain abstinent from heterosexual activity*, or

2. Agrees to use (or have their partner use) acceptable contraception to prevent pregnancy within the projected duration of the trial 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 intra-uterine 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).

*Abstinence can be used as the sole method of contraception if it is in line with the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ethics committees. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, postovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

4.2. Exclusion Criteria

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

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

2. 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).

3. Subjects who are <80% compliant based on pill count with the Placebo Run-in medication.

4. History of myocardial infarction, unstable angina, arterial revascularization, stroke, transient ischemic attack, or New York Heart Association (NYHA) functional class III-IV heart failure within 3 months of S1.

5. 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 S1, confirmed via 1 repeat triplicate set at S1 if deemed necessary by investigator's judgement. For subjects with a confirmed mean triplicate value of sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg at the S1 visit, the Investigator and/or treating physician is allowed to adjust background blood pressure medication(s) to improve blood pressure control in order for the subject to have blood pressure re-measured to determine study eligibility.

6. Subject has a clinically significant electrocardiogram (ECG) abnormality at S3 that requires further diagnostic evaluation or intervention (eg, new, clinically significant arrhythmia or a conduction disturbance).

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

8. 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.

9. 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.

10. Any clinically significant malabsorption condition.

11. Meets any of the following criteria:

    - Subject is on a weight-loss program and is not weight-stable.
    - Subject is on a weight-loss medication (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.

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

12. Subject who had bariatric surgery within 12 months of S1 or bariatric surgery >12 months from S1 but is not weight stable.

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

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

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. This will be assessed at each of the screening visits (S1, S2 and S3 as applicable per flowchart [FPG or finger-stick measurement]).

16. At the Day 1 visit (Visit 4), subject has a fasting finger-stick glucose (FFSG) <120 mg/dL (6.7 mmol/L) or >270 mg/dL (15.0 mmol/L).

    Note: If the subject meets this exclusion criterion AND the investigator believes that the value is not consistent with the subject's current self-monitoring blood glucose (SMBG) values and S3/Week -2 FFSG value, the subject should not be excluded at this time. This visit should be changed to an Unscheduled Visit and the subject should be rescheduled for Visit 4/Day 1 within 7 days. Additional single-blind placebo run-in medication should be dispensed if needed. If the subject meets this FFSG exclusion criterion at the rescheduled Visit 4/Day 1, the subject MUST be excluded.

17. Fasting serum triglyceride >600 mg/dL (6.8 mmol/L) at S1, confirmed by a single repeat if deemed necessary by investigator's judgement. For subjects with confirmed fasting triglycerides >600 mg/dL, the Investigator and/or treating physician is allowed to adjust the background lipid altering medication(s)/regimen to lower fasting triglycerides in order for the subject to having fasting triglycerides re-measured to determine study eligibility.

18. Subjects taking blood pressure or lipid altering medications that have not been on a stable dose for at least 4 weeks prior to randomization.

19. Subjects who are currently being treated for hyperthyroidism.

20. Subjects who are on thyroid replacement therapy and who have not been on a stable dose for at least 6 weeks prior to randomization and/or subjects who have a thyroid-stimulating hormone (TSH) outside of the laboratory reference range at S1.

21. Male subjects with a serum creatinine ≥1.3 mg/dL (≥115 μmol/L) or female subjects with a serum creatinine ≥1.2 mg/dL (≥106 μmol/L) or subjects with an eGFR <55 mL/min/1.73m^2 according to the 4-variable Modification of Diet in Renal Disease (MDRD) equation at S1.

22. An aspartate transaminase (AST) or alanine transaminase (ALT) >2X the upper limit of normal (ULN) range at S1, or a total bilirubin >1.5 X the ULN unless the subject has a history of Gilbert's.

23. 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.

24. Use of the following prohibited therapeutic agents. These agents are not to be used from 12 weeks prior to S1:

    - Insulin of any type (except for short-term use during concomitant illness or other stress).
    - Other injectable anti-hyperglycemic agents (eg, pramlintide, exenatide, liraglutide).
    - Another SGLT2 inhibitor.
    - Bromocriptine.
    - Colesevelam.
    - Rosiglitazone or pioglitazone.
    - Any other anti-hyperglycemic therapy with the exception of the protocol-approved agents.

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 Placebo Run-in Period (S3/Day -14) to the last dose of investigational product.

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

26. 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 or Merck employees directly involved in the conduct of the trial.

27. Participation in any other trials involving investigational drug(s) (Phase 1-4) within 30 days before S1 and/or has plan of participating any other trials during study participation.

28. Subjects who have undergone a surgical procedure within 6 weeks prior to signing informed consent or have planned major surgery during the trial. Note: A subject who has undergone minor surgery within the 6 weeks prior to S1 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.

29. At the randomization visit, 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.

30. 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.

31. 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 investigational product.

32. Subjects who have donated blood or blood products within six weeks of S1 or who plan to donate blood or blood products at any time during the trial.

33. Subjects with Human Immunodeficiency Virus (HIV) assessed by medical history.

34. Subjects with:

    - Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells, or

    - Clinically important hematological disorders (such as aplastic anemia, myeloproliferative or myelodyplastic syndromes, thrombocytopenia).

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

4.3. Randomization

Subjects who meet eligibility criteria will be assigned a unique identifier via an Interactive Voice Response System (IVRS) at S1, which will be retained throughout the duration of their participation in the trial. A computer-generated randomization code using the method of random permuted blocks will be utilized to assign subjects on Day 1 (V4) to 1 of the 3 treatment regimens (ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo).

There will be two stratification groups at randomization – 'China' and 'Other'. Randomization to the China stratum will be capped at approximately 396 subjects. and randomization to the 'Other countries' stratum will be capped at approximately 99 subjects.

4.4. Life Style Guidelines

4.4.1. Subject Management Prior to Scheduled Visits

- Subjects must abstain from all food and drink (except water) at least 10 hours prior to any blood sample collections for clinical laboratory tests, fasting glucose and the start of pharmacokinetic assessments.

- 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 visits to the site, subjects must be instructed to arrive without having taken the dose of investigational product, open-label metformin, or rescue therapy (if applicable). Other medications may be administered prior to the clinic visit if they can be administered without food. 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 activity.

4.4.2. Dietary Counseling

Subjects will be counseled on appropriate dietary and lifestyle guidelines for T2DM at S2 and asked to maintain these guidelines throughout participation in the trial.

Counseling on dietary guidelines should be in accordance with local medical standards of care for subjects with T2DM.

4.4.3. Physical Activities

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

4.4.4. Alcohol, Caffeine and Tobacco

- Intake of alcohol should be limited (refer to exclusion 9 for acceptable amount of alcohol consumption).

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

4.5. Female Contraception

Only female subjects of non-childbearing potential, and females of childbearing potential who agree to use adequate methods of contraception, as outlined below in Section 4.5.2 will be allowed to enroll in this trial.

4.5.1. Females– Non-childbearing Potential

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

- Postmenopausal: defined as at least 12 months with no menses in women ≥45 years of age, or
- Has had a hysterectomy and/or bilateral oophorectomy, or had bilateral tubal ligation or occlusion at least 6 weeks prior to S1.

4.5.2. 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 while the subject is receiving investigational product and for 14 days after the last dose of investigational product.

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).

4.6. Sponsor Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. 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 help desk 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 help desk 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 study 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 help desk 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 TREATMENT

5.1. Allocation to Treatment

Approximately 495 subjects will be randomized in a 1:1:1 ratio to receive ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo once daily.

Allocation of subjects to treatment groups will proceed through the use of a computerized Interactive Voice Response System (IVRS) that is accessible 24 hours per day, 365 days per year. The dispenser will be required to enter or select information as will be specified by the IVRS user manual. Subject information will be entered into the system starting at S1 when the subject will be assigned a unique identifier which will be retained throughout the duration of participation in the trial. On Day 1 (V4), once the inclusion, exclusion and randomization criteria have been verified, each subject will be assigned 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

At the initiation of the trial, the sites will be instructed on the method for breaking the blind if required for urgent subject management. The method will be an electronic process via IVRS. Blinding codes should only be broken in emergency situations for reasons of subject safety (ie, when the unblinding information is considered clinically necessary for appropriate subject management). Whenever possible, the Investigator or sub-Investigator should consult with a member of the Sponsor study 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. Blinded investigational product will be assigned to subjects via an IVRS or equivalent.

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

5.3.2. Placebo Run-in

A single-blind placebo tablet run-in will be administered starting at Day -14/Visit S3 where subjects will be instructed to take 1 tablet of placebo matching ertugliflozin 5 mg and 1 tablet of placebo matching ertugliflozin 10 mg each day from the bottles provided for this period. The last dose of placebo run-in investigational product should be taken on the day prior to Day 1. Subjects should not be informed that they are taking placebo during this period. Subjects who are <80% compliant based on pill count with the Placebo Run-in medication will be ineligible for randomization.

5.3.3. Concomitant Metformin

Subjects will use the background metformin prescribed by their physician and provided in the local commercial packaging. Immediate Release (IR) or Extended Release (ER) forms are allowed in the study. Subjects should remain on the same formulation (IR or ER) of metformin from S2 to the Week 26 visit.

Metformin titration will be required for some subjects between S2 and S3, prior to the placebo run-in period. This will occur in subjects who have been receiving metformin monotherapy at a dose <1500 mg/day at S1 or who have been receiving metformin at a dose <1500 mg/day plus another AHA at S1.

The metformin dose should generally be increased by 500 mg per week (or as standard practice per the Investigator) to achieve the maximally approved/tolerated dose referring to the label, which must be ≥1500 mg/day. Metformin should generally be taken with meals. Those subjects will enter the placebo run-in period at S3 after the monotherapy dose of ≥1500 mg/day has been kept stable for at least 8 weeks.

The metformin dose will not be changed from S3 until the end of the trial (V8), except if medically necessary. In that case, all efforts should be made to get the subject back to the dose at randomization.

5.3.4. Administration of Double-Blind Investigational Product

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 will be dispensed 2 bottles and given clear dosing instructions. They will be instructed to take 2 tablets per day of double-blind investigational product, one from each bottle, as follows. Subjects randomized to ertugliflozin 5 mg will receive 1 ertugliflozin 5 mg tablet and 1 placebo ertugliflozin 10 mg tablet per day. Subjects randomized to ertugliflozin 15 mg will receive 1 ertugliflozin 5 mg tablet and 1 ertugliflozin 10 mg tablet per day. Subjects randomized to placebo will receive 1 placebo ertugliflozin 5 mg tablet and 1 placebo ertugliflozin 10 mg tablet per day.

The investigational product should be taken orally at approximately the same time of day in the morning from Day 1 through to Week 26 (last dose taken the morning prior to the Week 26 visit) or early termination. In addition, subjects will be instructed to delay the self-administration of investigational product on the day of their visits, when the visit assessments should be completed prior to administration. On Day 1, Week 12 and Week 18 visit days, subjects will take the dose of double-blind investigational product in the clinic after visit assessments.

If a subject misses a dose of investigational product during the trial, he/she should be instructed to take it as soon as the subject remembers unless it is time for the next dose. Subjects should be instructed not to "make up" for the missed dose by taking two doses at the same time.

5.3.5. 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 with the placebo run-in medication should be monitored by study personnel at the site, at the end of the placebo run-in (Day 1/Visit 4), by comparing the returned investigational product with the amount dispensed and the information reported by the subject. The number of tablets issued minus the number of tablets returned will be used to calculate tablets taken. From this information, compliance will be calculated as:

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

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

During the remainder of the trial, compliance for subjects must be assessed for the ertugliflozin/matching placebo by taking the subject's report.

The Investigator or designee will counsel subjects who report taking <80% of the prescribed medication (s) described above following randomization. The Investigator or designee will determine factors that resulted in <80% compliance with these medication(s) and will take steps to improve compliance. Subjects will continue these medications but will be counseled on the importance of taking their medication(s) 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 the drug label and applicable regulatory requirements.

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

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 AHAs taken by the subject at any time prior to S1, and any other medications taken within 8 weeks prior to S1, will be recorded on the appropriate electronic case report form (eCRF). The site may rely on subject report for this information. Concomitant medications taken during the trial must also be recorded. All subjects must be questioned about concomitant medication according to the Schedule of Activities.

Medications that are indicated as prohibited in the Exclusion Criteria must not be used prior to or during the trial as specified in Section 4.2. Such prohibited medications include use of any other anti-hyperglycemic therapy with the exception of the protocol-approved agents as well as pharmacological doses of corticosteroids as described in Section 4.2.

Subjects who are not on a stable dose of blood pressure or lipid altering medications at S1 can be scheduled appropriately for S3 and Day 1 to ensure they have a stable dose for at least 4 weeks prior to randomization per the exclusion criterion. Subjects who are not on a stable dose of thyroid replacement at S1 can be scheduled appropriately for S3 and Day 1 to ensure they have a stable dose for at least 6 weeks prior to randomization per exclusion criterion 20. To the extent that is reasonable, the Investigator should make all efforts to modify these regimens in advance of randomization to avoid the need to change after randomization.

However, the Investigator or subject's physician/health care provider is permitted to make adjustments in blood pressure or lipid altering background therapy throughout the trial if clinically required.

Initiation of a weight-loss medication during the study (eg, orlistat, phentermine, topiramate, lorcaserin) is prohibited. **Note**: Subjects who are on treatment with a weight-loss medication or other medication associated with weight changes (eg, anti-psychotic agents) and who are weight-stable (ie, <5% change in body weight within 6 months of S1) are eligible to participate in the study and permitted to continue these medications during the study.

The use of herbal supplements and other natural products (including Traditional Chinese Medicine) should be discouraged. Subjects who do not discontinue the use of such supplements or natural products prior to the S3 visit/Week -2 or combined visit S2/S3 should be instructed not to change the use or dose of the product during the trial. Subjects should be instructed not to initiate new supplements during the trial. Any use of herbal supplements or Traditional Chinese Medicine will be captured in the eCRF.

5.6. Glycemic Rescue Therapy

Subjects will be prescribed open-label glycemic rescue therapy with glimepiride with initial dose and titration managed according to physician judgment, if they meet specific, progressively more stringent, glycemic thresholds based on a **repeated, confirmed** FPG measured by the **central lab** according to the directions below:

Table 4. Glycemic Thresholds

After Randomization (Day 1) 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 26:	FPG >200 mg/dL (11.1 mmol/L)

Subjects who meet the glycemic rescue thresholds detailed in Table 4 should have the repeat FPG measurement performed as early as possible (within 7 days following the receipt of test results).

Glycemic rescue therapy with glimepiride must be initiated at a rescue visit which is either a scheduled or an unscheduled visit at the investigational site, and not by a telephone visit. The investigator will determine initial dose and manage glimepiride titration as clinically appropriate and consistent with the country-specific product label. At the rescue visit, immediately prior to initiation of glycemic rescue therapy, subjects meeting rescue criteria must undergo the procedures described in Section 6.5.

Subjects requiring glycemic rescue therapy are to remain in the trial (unless they meet discontinuation criteria) up to their trial completion by Week 26 (or Early Termination), and will continue to receive background metformin (same dose and regimen) and blinded investigational product (ertugliflozin/placebo).

5.6.1. Drug Supplies for Glycemic Rescue Therapy

Open-label glimepiride will be supplied locally by the trial site or subsidiary, depending on local country operational or regulatory requirements.

6. STUDY PROCEDURES

For the procedures described below, where multiple procedures are scheduled at the same time point(s) relative to dosing, 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 performed before or after blood specimen collection.
- Visit windows for this trial are recommended, not required.
- On scheduled visits to the site, subjects must be instructed to arrive without having taken the dose of investigational product, open-label metformin, or rescue therapy (if applicable). Other medications may be administered prior to the clinic visit if they can be administered without food. 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 activity.

6.1. Instructions to Subjects

At the S2 visit, subjects will be given the following instructions/guidance to be complied with for the duration of participation in the trial up to Week 26 visit (or early termination) and provided the following or similar items to aid in 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 with a minimum of 2 determinations per week.
    - Home glucose monitoring should be undertaken in the event subjects experience symptoms of hyperglycemia or hypoglycemia.
    - During the run-in period, subjects should be counseled to contact the trial site if fingerstick glucose levels are above 260 mg/dL (14.4 mmol/L) ≥2 times per week. Subjects will be instructed to contact the site if their fingerstick glucose values are ≤70 mg/dL (≤3.9 mmol/L). Furthermore, in order to assess the need for rescue and/or discontinuation from blinded investigational product, subjects should be instructed to contact the site for fingerstick glucose values that are >270 mg/dL (15.0 mmol/L) after Visit 4/Randomization (Day 1) through Visit 5 (Week 6), or >240 mg/dL (13.3 mmol/L) after Visit 5/Week 6 through Visit6/Week 12, or >200 mg/dL (11.1 mmol/L) after Visit 6/Week 12.

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

At S2 or combined S2/S3, 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, palpitation, 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 episodes he or she believes may represent hypoglycemia. If a fingerstick glucose has been obtained before or shortly (ie, within a few minutes) after treating, the value should be recorded in the log. In addition, subjects will be instructed to record in the log any fingerstick glucose values ≤70 mg/dL (3.9 mmol/L) regardless of the presence of 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 on the log. Each episode should be evaluated by the Investigator. For episodes determined to be hypoglycemia (symptomatic or asymptomatic), and for all glucose values ≤70 mg/dL (3.9 mmol/L) regardless of whether they are considered an adverse event, the hypoglycemia assessment (HA) electronic case

report form (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 S2 or combined S2/S3 visit only; monitoring at other visits may be done by other appropriate site personnel evaluating the subject.

At S2 or combined S2/S3, the subject will receive counseling on a diet that is consistent with the local guidelines of the country of the investigational site. At each subsequent visit, the subject will be asked about their diet and exercise. 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. Subjects must not engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) within 48 hours before clinic visits in which blood samples will be collected.

6.2. Screening

6.2.1. Screening Visit 1 (S1)

As subjects must be fasting for the S1 visit, it is permissible that the Informed Consent Document is signed by the subject prior to the S1 visit. Because some of the laboratory data at S1 can be repeated (see Exclusion Criteria), the S1 visit may actually occur over several days.

Subjects will be instructed to arrive at the site after a minimum **10-hour fast** (except water) for S1. 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).
- Contact IVRS.
- Provide subject with Study Contact Card.
- Collect demography, medical history including smoking status as well as prior medications used.
- Measure body weight and height in duplicate [refer to Section 7.2].
- Collect triplicate measurements of sitting blood pressure and pulse rate [refer to Section 7.4.2].

- Obtain blood and urine specimens for clinical laboratory tests [refer to Section 7.4.1] of:
  - Hematology, chemistry;
  - HbA1c, fasting plasma glucose (FPG), fasting triglycerides, TSH;
  - Urine pregnancy test for women of childbearing potential.
- Review of eligibility criteria.

Subjects must be instructed to continue their background oral AHA(s); no changes to background oral AHA (metformin or non-metformin plus single allowable AHA if applicable) will be made until the S2 Visit. Allowable AHA are: sulfonylurea, DPP-4 inhibitor, meglitinide, or alpha-glucosidase inhibitor.

6.2.2. Screening Visit 2 (S2)

A separate S2 visit is required for subjects taking metformin monotherapy for less than 8 weeks at the S1 visit and for those who require a change to their diabetes regimen at S2 (including subjects who need to discontinue their AHA therapy). Subjects whose HbA1c at S1 is 7.0-10.5% (53-91 mmol/mol), and are on metformin monotherapy at a stable dose of ≥1500 mg/day for 8 weeks or more at S1 can proceed to a **combined S2/S3 Visit**. For combined visits, all procedures from each individual visit must be performed at the one combined visit.

Subjects on a stable dose of metformin monotherapy ≥1500 mg/day <8 weeks at S1 will enter a dose stable period, so that they will have received at least 8 weeks of a stable dose of metformin monotherapy prior to S3 and entering the placebo run-in period. For subjects receiving metformin monotherapy <1500 mg/day, the metformin dose must be titrated to ≥1500 mg/day and maintained at a stable dose for at least 8 weeks before the placebo run-in visit at S3. Subjects receiving metformin in combination with another single allowable AHA must discontinue this non-metformin AHA beginning at the S2 visit and remain off this other AHA for the duration of this trial, and if applicable, the metformin dose must be titrated to ≥1500 mg/day and maintained at a stable dose for at least 8 weeks before S3.

Approximately 1 week following the S1 visit, subjects will return to the site after a minimum **10-hour fast** (except water) for the S2 visit. The following procedures should be completed:

- Conduct inquiry about any spontaneously reported adverse events by asking the subjects to respond to a non-leading question such as “how do you feel?”
- Obtain urine sample for urinalysis [refer to Section 7.4.1].
- Subjects will be given a sponsor-provided glucose meter, a self-monitoring blood glucose log and needed supplies to enable them to perform finger stick blood glucose monitoring at home. Subjects should be instructed on how to complete the log.

- As a means of confirming subjects' understanding of the instructions, subjects will perform a fasting finger stick blood glucose assessment while at the site.
- Subjects will be educated on the symptoms of hyperglycemia (eg, polyuria, polydipsia) and instructed to call the site should severe hyperglycemia symptoms occur/or if fingerstick glucose levels are above 260 mg/dL (14.4 mmol/L) ≥2 times per week [refer to Section 6.1].
- Subjects will be educated on the symptoms of hypoglycemia and instructed to call the site should severe hypoglycemia occur or an episode of fingerstick glucose ≤70 mg/dL (3.9 mmol/L) before next visit (ie, S3) [refer to Section 6.1.1]. Subjects will be provided with a hypoglycemia assessment log that they must use to track the incidence of hypoglycemia..
- Subjects will be counseled by a dietician or qualified health care provider on appropriate dietary and lifestyle guidelines for T2DM. Counseling on dietary guidelines will be in accordance with local medical standards of care for patients with T2DM.
- Review and update concomitant medications since last visit.
- Review of eligibility criteria.

6.2.3. Placebo Run-in (Visit S3 or Combined S2/S3)

A separate S3 visit is required for subjects taking metformin monotherapy for less than 8 weeks at the S1 visit and for those who require a change to their diabetes regimen (including subjects who need to discontinue their AHA therapy). Subjects whose HbA1c at S1 is 7.0-10.5% (53-91 mmol/mol), and are on metformin monotherapy at a stable dose of ≥1500 mg/day for 8 weeks or more at S1 can proceed with a **combined S2/S3 Visit**. If the S2 and S3 are combined as S2/S3, all procedures from each individual visit must be performed at the one combined visit.

Subjects will return to the site after a minimum **10-hour fast** (except water) for S3 or combined S2/S3. The following procedures should be completed:

- Update concomitant medications since last visit.
- Conduct inquiry about any spontaneously reported adverse events by asking the subjects to respond to a non-leading question such as “how do you feel?”
- Perform complete physical examination [refer to Section 7.3].
- Obtain supine, single, standard, 12-lead ECG [refer to Section 7.4.4].
- Obtain duplicate orthostatic blood pressure and pulse rate measurement (supine → standing) [refer to Section 7.4.3].
- Measure body weight in duplicate [refer to Section 7.2].

- Perform a fasting finger stick blood glucose assessment.
- Measure HbA1c to assess eligibility for subjects taking metformin monotherapy for less than 8 weeks at the S1 visit and for those that required a change to their diabetes regimen at the S2 visit (including subjects receiving <1500 mg/day of metformin at S1 and for subjects who have discontinued the non-metformin AHA therapy at the S2 visit).
- Urine pregnancy test for women of childbearing potential.
- Diet and exercise monitoring (see Section 6.1.2).
- Review self-monitoring blood glucose and Hypoglycemia Assessments logs completed by the subjects (refer to Section 7.4.6).
- Review of eligibility criteria.

Following completion of the above procedures:

- Contact IVRS.
- Provide subject with glucose meter supplies and additional self-monitoring blood glucose or hypoglycemia assessment logs, as needed.
- Placebo for placebo run-in will be dispensed and first dose should be administered and witnessed in clinic [refer to Section 5.3.2].

6.3. Double-Blind, Placebo-Controlled Treatment Period (Visits 4 through 8)

6.3.1. Day 1 (Visit 4)

At 14 days ±5 days relative to S3 (or combined S2/S3 visit), subjects will return to the site after a minimum **10-hour fast** (except water) for the Day 1 (V4). At this visit, the following procedures will be completed prior to administration of investigational product:

- Assessment of pill count on the returned bottles dispensed at the previous visit (S3) will be undertaken.
- Assess treatment compliance. If non-compliance to the blinded placebo is identified (ie, <80% of placebo run-in medication taken by subject), the subject **must not** be randomized.
- Update concomitant medications since last visit.
- Measure body weight in duplicate [refer to Section 7.2].
- Obtain duplicate orthostatic blood pressure and pulse rate measurement (supine → standing) [refer to Section 7.4.3].

- Collect triplicate measurements of sitting blood pressure and pulse rate [refer to Section 7.4.2].
- Conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?"
- Review self-monitoring blood glucose and Hypoglycemia Assessment logs completed by the subject [refer to Section 7.4.6].
- Perform a fasting finger stick blood glucose assessment (FFSG) at the clinic. If the FFSG <120 mg/dL (6.7 mmol/L) or >270 mg/dL (15.0 mmol/L) AND the investigator believes that the value is not consistent with the subject's current self-monitoring blood glucose (SMBG) values, the subject should not be excluded at this time. This visit should be changed to an Unscheduled Visit and the subject should be rescheduled for **Visit 4/Day 1** within 7 days. Additional single-blind placebo run-in medication should be dispensed if needed.
- For subject who had **Visit 4** rescheduled due to FFSG <120 mg/dL (6.7 mmol/L) or >270 mg/dL (15.0 mmol/L) in the previous visit, FFSG needs to be re-tested at this visit and only those whose re-test FFSG is eligible can proceed into the study. In such cases, the sites will need to repeat all Visit 4/Day 1 procedures.
- Diet and exercise monitoring (see Section 6.1.2).
- Review of eligibility criteria.
- Register/randomize subject into trial using IVRS [refer to Sections 4.3 and 5.1].
- Obtain blood and urine specimens for clinical laboratory tests [refer to Section 7.4.1] of:
  - Hematology, chemistry, urinalysis;
  - HbA1c, lipid panel, FPG;
  - Urinary albumin/creatinine ratio, urine pregnancy test (for women of childbearing potential) [refer to Section 7.1].

Following completion of the above procedures:

- Provide subject with glucose meter supplies and additional self-monitoring blood glucose or hypoglycemia assessment logs, as needed.
- Supply of investigational product will be dispensed and first dose from the new supply should be administered and witnessed in clinic [refer to Section 5.3.4].

6.3.2. Week 6 (Visit 5)

At Week 6 ±7 days relative to Day 1 (V4), subjects will return to the site after a minimum **10-hour fast** (except water) for V5. At this visit, the following procedures will be completed:

- Update concomitant medications since last visit.
- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Measure body weight in duplicate [refer to Section 7.2].
- Obtain duplicate orthostatic blood pressure and pulse rate measurement (supine → standing) [refer to Section 7.4.3].
- Collect triplicate measurements of sitting blood pressure and pulse rate [refer to Section 7.4.2].
- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "how do you feel?" Assess potential clinical events for adjudication [refer to Section 7.6].
- Diet and exercise monitoring (see Section 6.1.2).
- Review self-monitoring blood glucose and Hypoglycemia Assessment Logs completed by the subject [refer to Section 7.4.6].
- Obtain blood and urine specimens for clinical laboratory tests [refer to Section 7.4.1] of:
  - Chemistry, urine pregnancy test (for women of childbearing potential) [refer to Section 7.1], HbA1c and FPG.
  - Pharmacokinetics of ertugliflozin (on a plasma sample) [refer to Section 7.5.1] including collection of date/time of blood draw and date/time of last dose of investigational product. PK sample is to be collected approximately 24 hr following the prior day's dose and before administration of the current day's dose.

Following completion of the above procedures:

- Provide subject with glucose meter supplies and additional self-monitoring blood glucose or hypoglycemia assessment logs, as needed.
- Contact IVRS.
- Dispense glimepiride glycemic rescue therapy, if applicable.
- Dispense investigational product.

6.3.3. Week 12 (Visit 6)

At Week 12 ±7 days relative to Day 1 (V4), subjects will return to the site after a minimum **10-hour fast** (except water) for V6. At this visit, the following procedures will be completed:

- Update concomitant medications since last visit.
- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Measure body weight in duplicate [refer to Section 7.2].
- Collect triplicate measurements of sitting blood pressure and pulse rate [refer to Section 7.4.2].
- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "how do you feel?" Assess potential clinical events for adjudication [refer to Section 7.6].
- Review self-monitoring blood glucose and Hypoglycemia Assessment Logs completed by the subject [refer to Section 7.4.6].
- Diet and exercise monitoring [refer to Section 6.1.2].
- Obtain blood and urine specimens for:
  - Clinical laboratory tests [refer to Section 7.4.1] including chemistry, hematology, urine pregnancy test (for women of childbearing potential) [refer to Section 7.1], HbA1c and FPG.
  - Pharmacokinetics of ertugliflozin (on a plasma sample) [refer to Section 7.5.1] including collection of date/time of blood draw and date/time of last dose of investigational product. PK sample is to be collected approximately 24 hr following the prior day's dose and before administration of the current day's dose.
  - The dose of double-blind investigational product should be administered and witnessed in clinic [refer to Section 5.3.4], time of administration should be collected.

Following completion of the above procedures:

- Provide subject with glucose meter supplies and additional self-monitoring blood glucose or hypoglycemia assessment logs, as needed.
- Collect a PK sample 1 h after dose administration of double-blind investigational product for ertugliflozin/placebo (with an allowable time window up to 3 hours post dose).
- Contact IVRS.

- Dispense glimepiride glycemic rescue therapy, if applicable.
- Dispense investigational product.

6.3.4. Week 18 (Visit 7)

At Week 18 ±7 days relative to Day 1 (V4), subjects will return to the site after a minimum **10-hour fast** (except water) for V7. At this visit, the following procedures will be completed:

- Update concomitant medications since last visit.
- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Measure body weight in duplicate [refer to Section 7.2].
- Collect triplicate measurements of sitting blood pressure and pulse rate [refer to Section 7.4.2].
- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "how do you feel?" Assess potential clinical events for adjudication [refer to Section 7.6].
- Review self-monitoring blood glucose and Hypoglycemia Assessment Logs completed by the subject [refer to Section 7.4.6].
- Diet and exercise monitoring (see Section 6.1.2).
- Obtain blood and urine specimens for clinical laboratory tests [refer to Section 7.4.1] of:
  - Chemistry, urine pregnancy test (for women of childbearing potential) [refer to Section 7.1], HbA1c and FPG;
  - Pharmacokinetics of ertugliflozin (on a plasma sample) [refer to Section 7.5.1] including collection of date/time of blood draw and date/time of last dose of investigational product. PK sample is to be collected approximately 24 hr following the prior day's dose and before administration of the current day's dose.
  - The dose of double-blind investigational product should be administered and witnessed in clinic [refer to Section 5.3.4], time of administration should be collected.

Following completion of the above procedures:

- Provide subject with glucose meter supplies and additional self-monitoring blood glucose or hypoglycemia assessment logs, as needed.

- Collect a PK sample 1 h after dose administration of double-blind investigational product for ertugliflozin/placebo (with an allowable time window up to 3 hours post dose).
- Contact IVRS.
- Dispense glimepiride glycemic rescue therapy, if applicable.
- Dispense investigational product.

6.3.5. Week 26 (Visit 8) – Final Study Visit / Early Termination Visit

At Week 26 ±7 days relative to Day 1 (V4), subjects will return to the site after a minimum **10-hour fast** (except water) for V8. At this visit (or early termination visit), the following procedures will be completed:

- Contact IVRS.
- Assess treatment compliance with investigational product.
- Review and update concomitant medications since last visit.
- Measure body weight in duplicate [refer to Section 7.2].
- Obtain supine, single, standard, 12-lead ECG [refer to Section 7.4.4].
- Collect triplicate measurements of sitting blood pressure and pulse rate [refer to Section 7.4.2].
- Conduct brief physical examination which includes assessment of heart, lungs, abdomen and extremities.
- Obtain duplicate orthostatic blood pressure and pulse rate measurement (supine → standing [refer to 7.4.3].
- Conduct inquiry about any spontaneously reported AEs by asking the subjects to respond to a non-leading question such as "how do you feel?" Assess potential clinical events for adjudication [refer to Section 7.6].
- Review self-monitoring blood glucose and Hypoglycemia Assessment Logs completed by the subject [refer to Section 7.4.6].
- Diet and exercise monitoring (see Section 6.1.2).

- Obtain blood and urine specimens for clinical laboratory tests [refer to Section 7.4.1] of:
  - Hematology, chemistry, urinalysis, urinary albumin/creatinine ratio, urine pregnancy test (for women of childbearing potential) [refer to Section 7.1], lipid panel, HbA1c, FPG;
  - Pharmacokinetics of ertugliflozin (on a plasma sample) [refer to Section 7.5.1] including collection of date/time of blood draw and date/time of last dose of investigational product. PK sample is to be collected approximately 24 hr following the prior day's dose.

Subjects, who discontinue from the trial prematurely, should be reminded that they will be contacted via telephone by the Investigator/qualified designee according to the same schedule as if they were still taking investigational product and will be asked to return for a visit at the Week 26 visit unless they withdraw consent per Section 6.6.

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 per Section 7.6, if applicable. The phone call should be completed within a ±3 day window.

6.5. Rescue Visit, if applicable

Subjects who require rescue therapy per Section 5.6 must have glycemic rescue therapy initiated at either a scheduled or unscheduled visit and not by a telephone call. The following procedures are to be completed at a rescue visit:

- Review and update concomitant medications since last visit,
- Assess treatment compliance with investigational product and counsel subjects who have been <80% compliant [refer to Section 5.3.5].
- Measure body weight in duplicate [refer to Section 0].
- Collect triplicate measurement of sitting blood pressure and pulse rate [refer to Section 7.4.2].
- Obtain duplicate orthostatic blood pressure and pulse rate measurement (supine → standing) [refer to Section 7.4.3].
- Conduct brief physical examination which includes assessment of heart, lungs, abdomen and extremities.
- Obtain blood specimens for clinical laboratory tests [refer to Section 7.4.1] including chemistry, hematology, urinalysis, lipid panel, HbA1c (only if visit is at least 6 weeks after randomization) and FPG.

- Conduct inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?" Assess potential clinical events for adjudication [refer to Section 7.6].

- Review self-monitoring blood glucose and Hypoglycemia Assessment logs completed by the subject.

- Diet and exercise monitoring (see Section 6.1.2).

- Dispense glycemic rescue therapy with glimepiride. Dosing of open-label glimepiride is at the Investigator's discretion.

- Provide subject with glucose meter supplies and additional self-monitoring blood glucose or hypoglycemia assessment logs, as needed.

6.6. Subject Withdrawal

Subjects may withdraw from the trial 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.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. For withdrawn subjects, the Investigator should inquire about the reason for withdrawal, request the subject return all unused investigational product, request the subject to return for an early termination visit, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the trial, 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.

Subjects who discontinue treatment with blinded investigational product for reasons other than withdrawn consent should attend the clinic for a visit where all early termination procedures are performed followed by a post-treatment telephone call 14 days after the last dose of blinded investigational product. Thereafter, subjects will be followed by telephone contacts according to the study visit schedule until the end of the trial (Week 26), but will not have other procedures performed that are outlined in the study schedule of activities. The purpose of the telephone contacts, as well as the 14-day post-treatment telephone call, is to collect information about subjects' health status (ie, evaluate if the subject experienced any SAEs or events eligible for adjudication [see Section 7.6]).

If a subject indicates his or her intention to stop active participation in the trial (ie, chooses to no longer attend visits at the investigational site, take blinded investigational product, and have other study-related procedures conducted at the investigational site), or if the Investigator has recommended stopping the investigational product, the Investigator must

clarify with the subject if he/she is willing to continue in the study with contact at intervals to provide a brief and focused update on health status (eg, SAEs and events eligible for adjudication [see Section 7.6]). It will be important for the subject to understand the importance of complete collection of information, and also the limited requirements for continuing to provide this information (ie, a brief telephone contact, occurring at the time of the originally planned study visits). Thus, subjects may discontinue investigational product and continue in the study with clinic visits or allow continued site contacts without clinic visits, or they may indicate that they do not wish to have further contact with the site.

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 collection of information on clinical cardiovascular events. This may include contacting family members and health care providers and, when applicable, using subject location services. 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. All attempts to contact a subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, requests the subject to return all unused investigational product(s), requests the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

Subjects who are discontinued from investigational product but agree to continue to participate in the trial by providing follow-up information can have medical and diabetes management by their managing physician or Investigator, as appropriate. These subjects may initiate any other therapy as needed (previously prohibited medications may be used). After discontinuation of investigational product, Pfizer or its designee will continue to reimburse/supply (as specified in Section 5.6.1), glimepiride (for those rescued) until Week 26. The Investigator should ensure that the subject has enough open-label rescue medication until the next scheduled in clinic visit (if applicable). Procurement of any other AHAs is the responsibility of the subject.

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

Reasons for protocol-specified discontinuation from the investigational product or from the trial are listed, but not limited, 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 delegate] assessment) for any laboratory safety test abnormality resulting in discontinuation from investigational product.

Withdrawal from the Trial

- Subject requests discontinuation from the trial (ie, refuses to continue to be contacted to provide further health information).
- Death.

Discontinuation of Investigational Product

1. Subject meets protocol-specified hyperglycemia criteria as specified below:

   Subject has been rescued with glimepiride and is on the maximum labeled or maximum-tolerated dose (if lower than the maximum labeled dose) for at least 4 weeks, and continues to meet glycemic thresholds specified in Table 4 for the relevant time point in the trial, without a reasonable explanation (eg, intercurrent illness or medication omission).

2. Hypoglycemia: Repeated (2 or more episodes since the prior visit) FPG or fingerstick glucose <50 mg/dL (<2.8 mmol/L) with or without symptoms of hypoglycemia or ≤70 mg/dL (≤3.9 mmol/L) with symptoms of hypoglycemia, and without a reasonable explanation (such as increased physical activity or skipped meal) or with a reasonable explanation and likely to reoccur.

   Note: For subjects rescued with glimepiride, the protocol-specified discontinuation criteria for hypoglycemia only apply after the subject has interrupted glycemic rescue medication.

3. Abnormal liver function tests meeting discontinuation criteria specified in Section 8.7.

4. Parameters of Renal Function:

   - Serum creatinine concentrations consistently ≥1.5 mg/dL (133 µmol/L) in men or ≥1.4 mg/dL (123 µmol/L) in women.

   OR

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

   Note: A consistent value is defined as a repeat measurement performed within 7 days of notification from the central laboratory. If the eGFR or serum creatinine value continues to meet discontinuation criterion but demonstrates improvement relative to the prior result, an additional repeat may be performed (within 7 days). If this repeat continues to meet the discontinuation criteria, the subject must be discontinued from investigational product. See Section 6.6.1.1 for guidance on following subjects who discontinue due to decreased renal function or renal-related adverse events.

5. Requirement for one of the prohibited medications listed in Section 5. Subjects temporarily placed on a prohibited medication by a non-study physician that has been stopped and which is not clinically necessary may continue in the study.

6. For subjects who are on glycemic rescue medication, and found to be hypersensitive to or intolerant to glimepiride or if such a subject develops any condition for which glimepiride is contraindicated in accordance with the local drug label of the country where the subject is participating.

7. Pregnancy.

   Note: A positive urine pregnancy test requires immediate interruption of investigational product until serum 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.

8. 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.

9. Subjects undergoing bariatric surgery.

10. The Investigator or subject are unblinded to randomized assignment (eg, unblinding information obtained through IVRS or inadvertently obtained).

11. Subject's decision: Subject no longer agrees to actively participate in the study (ie, take blinded investigational product or other required concomitant study medication, attend study visits, or otherwise comply with study procedures) but agrees to be contacted at times of regular study visits to collect health status (ie, SAEs and adjudicated events).

If a subject discontinues investigational product, he/she should complete all Early Termination Visit procedures as described in Section 6.3.5 and listed in Schedule of Activities. Unless the consent to follow the subject is specifically withdrawn, a subject will be contacted via telephone by the Investigator/qualified designee according to the same schedule as if he/she were still taking investigational product and will be asked to return for a visit at Week 26. Such subjects may initiate other AHA therapy as indicated (prohibited medications described in Section 5.5 will not apply to these subjects.)

6.6.1.1. Follow-up for Subjects who Discontinue Due to Decreased Renal Function

Subjects who discontinue blinded investigational product for eGFR/creatinine discontinuation criteria (see Section 6.6.1) or renal-related adverse events should have a repeat eGFR/creatinine performed approximately 1 week after the last dose of Investigational Product. This post-treatment visit may occur at the Early Termination visit (if the Early Termination visit occurs 1 week after the last dose of Investigational Product) or at an unscheduled visit. The out of range test(s) should continue to be repeated at intervals, as considered appropriate (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 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, angiotensin-converting enzyme (ACE) inhibitors, diuretic agents, etc), and clinical assessment of volume

status (eg, measurement of orthostatic heart rate [HR] and blood pressure [BP], and physical examination focused on assessment of volume status); additional evaluations, including renal ultrasound, and microscopic urinalysis (with culture and sensitivity if infection is considered possible), urine creatinine and electrolytes, should be performed, as clinically appropriate.

7. 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 study team will be informed of these incidents in a timely fashion.

All biological samples will be assayed, by a sponsor-identified central laboratory, using a validated analytical method in compliance with the Sponsor's standard and validated methodologies, and 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. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test with a sensitivity of at least 25 mIU/mL will be performed at both the S1 and S3 Screening Visits and before investigational product administration at the Baseline visit 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 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 withdrawn from investigational product but may continue to be contacted according to the same schedule as if he/she were still taking investigational product and will be asked to return for a visit at the Week 26 visit. Pregnancy tests may also be repeated as per request of IRB (institutional review board)/IEC (independent ethics committee)s or if required by local regulations.

7.2. 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 are allowed to 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 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 conduct accuracy checks on the scale, the study 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 must be conducted approximately monthly, and the accuracy check record must be sent to the Sponsor at the end of the trial.

7.3. Physical Examinations

A complete physical examination will be performed at the S3 Visit. A brief physical examination including assessment of the heart, lungs, abdomen, and extremities will be performed at other times as listed in the Schedule of Activities. Abnormalities considered clinically significant should be reported as AEs. Other body systems may be evaluated as per the judgment of the Investigator or as needed to evaluate adverse events.

7.4. Safety

7.4.1. Clinical Laboratory Tests

The tests outlined in Table 5 will be performed at the pre-specified time points outlined in the Schedule of Activities following an overnight fast of at least 10 hours (except water).

The FPG and HbA1c results from the central laboratory will be masked at randomization and throughout the duration of the trial for both the sponsor and investigative site unless the results meet pre-specified alert criteria. A confirmatory plasma glucose value from the central laboratory on a new plasma sample will be required to make a final determination as to whether a subject meets the criteria for glycemic rescue or discontinuation. If it is confirmed a subject meets glycemic rescue or discontinuation criteria, FPG and HbA1c will be unmasked for the remainder of the trial.

Table 5. Clinical/Safety Central Laboratory Tests

Hematology	Chemistry	Urinalysis[a, e]	Others
Hemoglobin Hematocrit RBC Count Platelet Count WBC Count Total Neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Serum Creatinine Ca^{++} (total) Na^{+} K^{+} Cl^{-} Total CO_2 (Bicarbonate) Mg^{++} Phosphate Uric Acid AST (SGOT) ALT (SGPT) Alkaline Phosphatase Total bilirubin Direct (conjugated) bilirubin[b] Indirect (unconjugated) bilirubin[c] Albumin Total Protein	pH Protein (qual) Blood (qual) Ketones Leukocyte esterase Nitrites Microscopy[d]	*At S1 only:* - Fasting triglycerides/TSH At selected visits, only (refer to Schedule of Activities): -HbA1c - FPG -Urinary albumin/creatinine ratio[e] - Pregnancy tests (where applicable) - Lipid panel (ie, total cholesterol, HDL, LDL, non-HDL-C, triglycerides)

a. Samples collected for urinalysis will be sent to the central laboratory for dipstick analysis (not including uninary glucose assessment) and microscopy if needed, see [d].
b. Direct bilirubin measured only when total bilirubin is greater than upper limit of normal.
c. Indirect bilirubin measured only when total bilirubin is greater than upper limit of normal.
d. Microscopy to be performed by central laboratory if dipstick is positive for blood, nitrites, leukocytes and/or protein.
e. Urine sample(s) for urinalysis and albumin:creatinine ratio should not be obtained if the subject is menstruating, has vigorously exercised within 24 hours or had fever or an active infection within 2 days of the visit. Under these circumstances, the subject should provide a urine sample for evaluation at an unscheduled visit.

7.4.1.1. 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, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (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.

7.4.1.2. Urinary Albumin:Creatinine Ratio

A urine sample will be collected at the times listed in the Schedule of Activities 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.

7.4.2. Vital Signs (Sitting Blood Pressure and Pulse Rate)

Vital sign measurements include a triplicate measurement of sitting blood pressure and pulse rate. Blood pressure and pulse rate will be measured using an automated, oscillometric blood pressure measuring device at all time points noted in the Schedule of Activities. Site personnel should use the same blood pressure measuring device throughout the trial for each subject.

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

- Subjects will refrain from nicotine-containing products and/or ingesting caffeine for at least 30 minutes preceding the measurements.
- Subjects should be seated in a chair with their back supported, feet flat on the floor and arm bared (free of restrictions such as rolled up sleeves) and supported at heart level.
- The appropriate cuff size must be used to ensure accurate measurement. Each subject's cuff size should be noted in his/her source file to assure the same cuff size is used throughout the trial.
- Measurements should be taken on the same arm at each visit (preferably the non-dominant arm).
- Measurements should begin after at least 5 minutes of rest.
- The three measurements of both the blood pressure and pulse rate must be taken approximately 2 minutes apart with the triplicate set recorded in the source document and CRFs.
- 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.

7.4.3. Postural (Orthostatic) Blood Pressure and Pulse Rate

On the S3, Day 1, Week 6, Week 26 (or ET) and Rescue Visit, 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 at these clinic visits (except for S3 visit). 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:

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

7.4.4. Electrocardiogram, (12-lead ECG)

Single, supine 12-lead ECGs 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 procedure.
- 12-lead ECGs should be performed after the subject has rested quietly for **at least 10 minutes** in a supine position.

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

The ECGs performed at scheduled time points should be reviewed at the investigative site for subject eligibility confirmation and 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. Unscheduled ECGs (if needed per investigator judgment) will follow the same procedure and will be reviewed at the investigative site and be transferred to the central vendor for reading and interpretation.

Subject demographic information will be made available to the central scoring site that will provide results on heart rate (beats per minute [BPM]), overall interpretation, rhythm type, and heart rate intervals PR, QRS, QT, QTcB, and QTcF (msec), along with any comments.

7.4.5. 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 S2 visit.

7.4.6. Review of Hypoglycemia Assessment Logs

The site must review the hypoglycemia assessment logs completed by the subjects at **each** site visit subsequent to the S2 visit. Based on this information, an assessment of any symptomatic occurrence of hypoglycemia must be undertaken and appropriate decisions should be made by the Investigator.

7.4.6.1. 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, palpitation, tachycardia, tremulousness, irritability, blurred vision, and disorientation. 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.

A subject should be discontinued from the investigational product [refer to Section 6.6.1] if they have repeated (2 or more episodes since the prior visit) FPG or fingerstick glucose <50 mg/dL (<2.8 mmol/L) with or without symptoms of hypoglycemia or ≤70 mg/dL (≤3.9 mmol/L) with symptoms of hypoglycemia, and without a reasonable explanation (such as increased physical activity or skipped meal) or with a reasonable explanation and likely to reoccur.

Any episode of hypoglycemia must be captured on the Hypoglycemic Adverse Assessment Form of the CRF (refer to Section 6.1.1). For definition of hypoglycemic episode and severity categorization, refer to Section 7.4.6.1.1 below.

7.4.6.1.1. Definition and Severity Categorization of Hypoglycemic Events

Based on review of the subject completed hypoglycemia assessment logs at each outpatient visit to the site, the Investigator must assess the glucose values as well as any symptoms documented. Each hypoglycemic event will be reported by the Sponsor according to the following categories.

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. Finger-stick 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 finger-stick 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 finger-stick or plasma glucose concentration ≤70 mg/dL (3.9 mmol/L).

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

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

7.4.6.1.2. 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 glucose value ≤70 mg/dL (3.9 mmol/L) from either a fingerstick or central laboratory sample 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).

7.4.7. Assessment of Infections

7.4.7.1. Urinary Tract Infections

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

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

7.4.7.2. 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.

7.5. Pharmacokinetics of Ertugliflozin

7.5.1. Plasma for PK Analysis

On the morning of any visit that includes pharmacokinetic sampling, investigational product dosing (if applicable) will occur after the pre-dose sample is taken.

Blood samples (approximately 4 mL) to provide approximately 2 mL of plasma for pharmacokinetic analysis will be collected at visits specified in the "Schedule of Activities". Pre-dose samples will be collected at Weeks 6, 12, 18 and 26. In addition, post-dose samples will be collected at Weeks 12 and 18, 1 hour after administration of investigational product (but with an allowable window up to 3 hours). The exact date and time of the blood draw and the date and time of the last dose of investigational product reported by the subject prior to the blood draw should be captured on the CRF.

Samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C (if a refrigerated centrifuge is not available, place sample in an ice water bath for at least 10 minutes before centrifugation). The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C within 1 hour of collection.

Detailed instructions for the preparation and shipment of the samples can be found in the Laboratory Manual supplied by the central laboratory.

7.6. Clinical Event Adjudication

7.6.1. Clinical Cardiovascular Events, Venous Thromboembolic Events and All Deaths

The identification of potential clinical cardiovascular events (specified below), venous thromboembolic event and all deaths 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.

Cardiovascular disease is a major cause of mortality for subjects with T2DM. In order to evaluate the cardiovascular safety of ertugliflozin and to meet US and European Union regulatory requirements for the assessment of cardiovascular safety of any new diabetic therapy, selected serious cardiovascular events (specified below) 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 Endpoint Adjudication Committee (EAC) will be comprised of an external panel of independent physicians experienced in assessing cardiovascular endpoints. In addition, venous thromboembolic events, and hospitalization due to CHF will also be

adjudicated, to assure a comprehensive assessment of potentially significant cardiovascular events. 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 (ie, withdraws consent).

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 the 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.

The composite of adjudicated events of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (often referred to as major cardiovascular events [MACE]), plus hospitalization for unstable angina will contribute to a meta-analysis of cardiovascular safety of ertugliflozin across the Phase 2 and 3 programs. Events of venous thromboembolism/pulmonary embolism and hospitalized congestive heart failure (CHF) will be separately tabulated across the Phase III clinical development program, and are not included in the cardiovascular composite of MACE plus hospitalized unstable angina.

7.6.2. Fractures

In the Phase 2 study (B152006), following 12 weeks of dosing with ertugliflozin, there was a suggestion of an increase in markers of bone resorption,though there did not appear to be a clear dose-dependent effect with increasing dose of ertugliflozin. In totality, the clinical relevance of these findings remains unclear. However, the effect of ertugliflozin on bone mineral density will be evaluated in a Phase 3 trial. In addition, in this trial and throughout the Phase 3 program, all clinical fractures will be adjudicated by an external independent panel of physicians (radiologists) experienced in assessing fractures. The radiologists will review the radiograph(s) (if available) and, where applicable the local radiologist report and other source documents and confirm the presence of the fracture, location of fracture, number of fractures, and type of fracture (ie, high-trauma, low-trauma, pathological fracture, stress fracture, and other fracture). The panel will be blinded to treatment assignment. A Fracture Adjudication Charter will describe the precise mandates and procedures to be used for the adjudication of clinical fractures.

7.6.3. 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 be blinded to treatment assignment. A Pancreatitis Adjudication Charter will describe the precise mandates and procedures to be used for the adjudication of pancreatitis.

7.6.4. 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.

7.6.5. Renal Failure

Ertugliflozin, an SGLT2 inhibitor, increases urinary glucose excretion leading to an osmotic diuresis, and has the potential to reduce estimated glomerular filtration rate (eGFR), due to the effect on plasma volume (ie, a hemodynamic effect on eGFR). As part of the overall assessment of renal safety, events reported in this trial and throughout the Phase 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.

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

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

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

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 Pfizer or designee either by electronic media or paper. Appropriate 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 Pfizer or designee either by electronic media or paper. Appropriate 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 an other important medical event.

Refer to Table 6 for additional details regarding each of the above criteria.

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

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

8.5. Evaluating of Adverse Events

An Investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 6. The Investigator's assessment of causality is required for each adverse event. Refer to Table 6 for instructions in evaluating adverse events.

Table 6. Evaluating Adverse Events

Maximum Intensity	Mild	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death;** or	
	†**Is life threatening; or** places the subject, in the view of the Investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer; or	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	

Table 6. Evaluating Adverse Events

Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an Investigator who is a qualified physician. The Investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the Investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship to Sponsor's Product (continued)	The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)

Table 6. Evaluating Adverse Events

	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.)

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 Pfizer or designee either by electronic media or paper. Appropriate 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, 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 FDA (Food and Drug Administration) 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 product has an ALT or AST elevation beyond the clinical significant margin above, the Investigator should monitor the subject according to the instructions below and discontinue the subject from investigational product if a pre-specified criterion is met.

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

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

A) Subject has:

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

1. The subject should *interrupt* investigational product.
2. Refer to the "*Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials*" (located in the Investigator Trial File Binder or equivalent) and perform procedures accordingly.
3. If an etiology for the elevated ALT or AST and TBL levels is established and the abnormalities resolve, investigational product may be restarted with approval by the Sponsor. Otherwise, the subject should discontinue treatment with investigational product.

Note: Laboratory assessments prescribed in the *Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials* may be sent locally in emergent cases and to support subject compliance with the necessary evaluations. Subjects unwilling to undergo the prescribed testing should be discontinued from treatment with investigational product.

B) Subject has:

- **ALT or AST ≥8X ULN *OR***
- **ALT or AST ≥3X ULN and signs or symptoms of a drug reaction consistent with liver injury (eg, fever, eosinophilia, right upper quadrant pain, dark urine, fatigue, etc.)**

1. The subject should *interrupt* investigational product.
2. Perform repeat ALT and AST within 3 days of receipt of the laboratory report.
3. Initiate evaluation for potential causes. See Section II below.
4. Repeat ALT and AST tests at appropriate intervals, initially approximately 2-times per week, until resolution or return to baseline.
5. If an etiology for the elevated liver enzymes is established (eg, active hepatitis with specific etiology demonstrated, cholecystitis, biliary obstruction), investigational product may be restarted with approval by the Sponsor. Otherwise, the subject should discontinue treatment with investigational product.

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 product.

C) Subject has:

- **ALT or AST ≥3X and <8X ULN**

1. For subjects with:

   ALT or AST ≥3X and <5X ULN:

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

   OR

   ALT or AST ≥5X ULN and <8X ULN:

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

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

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

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

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

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

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 product.

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

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

Section II: Guidance for Assessment of Potential Etiology

Questions to Assess Etiology

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

1. Has the subject recently:
   - Had a change in his/her pattern of alcohol use? Investigate historic pattern of alcohol use as well.
   - Administered an illegal drug(s) (including intravenous drugs)?
   - Been exposed to a chemical agent or other environmental toxin?
   - Consumed any unusual foods (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, non-alcoholic 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 by the Sponsor

All adverse events meeting SAE criteria (see Section 8.4.1 above) must be reported to the Sponsor within 24 hours of when the site is notified of the event. The following refers to Sponsor processing of SAEs, but does not impact Investigator responsibilities for reporting of any SAE.

Potential pre-specified cardiovascular SAEs will be submitted for adjudication to an independent EAC (see Section 7.6.1 for details).

The following potential cardiovascular SAEs will not be subject to expedited reporting by the Sponsor, even if reported as related to investigational product 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

All efficacy and safety analyses will be performed for the overall study population, as well as for the China subpopulation using the analysis methods described in Sections 9.2 and 9.3.

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The sample size determination is based on the primary endpoint, reduction in HbA1c from Baseline to Week 26, within the subjects enrolled from China. Assuming a standard deviation (SD) of 1.0%,[11-18] a sample size of 105 subjects from China per group (total of 315 subjects from China) provides approximately 95% power to detect a difference in HbA1c of 0.5% between each ertugliflozin dose and placebo (and approximately 90% power for detecting this difference for both doses vs. placebo) using a two-sided 0.05 alpha level test. To control the overall Type I error rate at 0.05 within each population (overall study

population and the China subpopulation) a sequential testing approach will be used across the primary and secondary efficacy endpoints for which hypotheses will be tested, and for the two doses of ertugliflozin. Assuming a drop-out rate of 20% at Week 26 [(ie, either subjects who discontinue from the study, discontinue administration of IP (Investigational Product) or subjects who take rescue medication and are censored], approximately 396 subjects from China (132 per group) will be randomized. Additionally, this study will have approximately 99 subjects from at least two other Asian countries.

The total sample size for this study is approximately 495 randomized subjects.

9.2. Efficacy Analysis

The primary analysis population for efficacy analyses will be the Full Analysis Set (FAS), which is defined separately for each analysis endpoint to include all randomized subjects who have received at least one dose of investigational product and have at least one measurement of the respective endpoint at any time during the trial including baseline and post-baseline time points. Post-glycemic rescue therapy data from subjects who receive rescue therapy prior to Week 26, as well as post-bariatric surgery data will be censored from efficacy analyses.

9.2.1. Analysis of Primary Endpoint

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

- Country (categorical) (Applicable only for the analyses of the overall study population)
- Treatment (categorical),
- Visit (categorical),
- Treatment by visit interaction (categorical),
- AHA status at study entry (binary),
- Baseline eGFR (continuous) Values above 120 mL/min per 1.73 m^2 will be set to 120 mL/min per 1.73 m^2.

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.[20] 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 between each dose of ertugliflozin and placebo in terms of mean change from baseline at the primary time point of Week 26 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. Methods to address the potential issue of large differences in sample size from different countries will be described in the SAP.

Sensitivity analyses will be performed to assess the robustness of the primary model. ANCOVA will be conducted utilizing the last observation carried forward as the dependent variable and including fixed factors for country (categorical), treatment (categorical), baseline HbA1c (continuous), AHA status at study entry (binary), baseline eGFR (continuous) (eGFR values above 120 mL/min per 1.73 m^2 will be set to 120 mL/min per 1.73 m^2). A per protocol analysis will also be pre-specified in the statistical analysis plan. Descriptive and graphical summaries by treatment group and time point will also be presented. The models utilized for the China subpopulation will not include country as a term.

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 within each population (the overall study population, and China subpopulation) (see below for sequence of testing for the overall population and the China subpopulation). Within each of these two populations, 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.

9.2.2. Analysis of Secondary Endpoints

The proportion of subjects with an HbA1c <7.0% (53 mmol/mol) at Week 26 will be analyzed using a logistic regression model with terms for country (categorical) (applicable only for the analyses of the overall study population), treatment (categorical), baseline HbA1c (continuous), AHA status at study entry, and baseline eGFR (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, systolic blood pressure and diastolic blood pressure will be analyzed separately by fitting constrained longitudinal data analysis models similar to that used for the primary endpoint. Sitting blood pressure collected in triplicate will be used for assessment of blood pressure as a secondary endpoint.

For the overall study population, the secondary efficacy endpoints of FPG, proportion of subjects with an HbA1c <7.0%, body weight, systolic blood pressure and diastolic blood pressure will be tested for each ertugliflozin dose versus placebo using a multiple testing procedure that strongly controls the overall Type I error rate at 0.05. For the China subpopulation, due to smaller sample size, which limits power for other secondary endpoints, only FPG and body weight endpoints will be tested for each ertugliflozin dose versus placebo using a multiple testing procedure that strongly controls the Type I error rate at 0.05. Therefore, a step-down hierarchical, sequential testing approach will be used, as follows:

Order (for Overall Study population)	Order (for China subpopulation)*	Endpoint (Change from Baseline to Week 26**)	Arm Comparison
1	1	HbA1c	15 mg ertugliflozin arm to placebo
2	2	HbA1c	5 mg ertugliflozin arm to placebo
3	3	FPG	15 mg ertugliflozin arm to placebo
4	4	FPG	5 mg ertugliflozin arm to placebo
5	5	Body Weight	15 mg ertugliflozin arm to placebo
6	6	Body Weight	5 mg ertugliflozin arm to placebo
7	N/A	HbA1c <7.0% at Wk 26	15 mg ertugliflozin arm to placebo
8	N/A	HbA1c <7.0% at Wk 26	5 mg ertugliflozin arm to placebo
9	N/A	Systolic BP	15 mg ertugliflozin arm to placebo
10	N/A	Systolic BP	5 mg ertugliflozin arm to placebo
11	N/A	Diastolic BP	15 mg ertugliflozin arm to placebo
12	N/A	Diastolic BP	5 mg ertugliflozin arm to placebo

* Hierarchical hypothesis testing for the China study population will only be performed for the HbA1c, FPG and body weight endpoints.
**Except for HbA1c <7.0% at Wk 26 endpoint.

Within each study population, starting with the first hypothesis, the test will be conducted at a 5% level of significance. If the hypothesis test is significant, then the next hypothesis within that study population will be tested at a 5% level of significance. Otherwise, testing ceases within this hierarchy within each study population. The testing sequence as specified above will be applied for the overall studypopulation and the China subpopulation. The non-numbered items listed above will be assessed with 95% CIs and nominal p-values.

9.2.3. Endpoints Related to Pharmacokinetics of Ertugliflozin

Details on the pharmacokinetic analysis may be found in the Statistical Analysis Plan. The pharmacokinetic data from this trial may be combined with data from other studies for population pharmacokinetic analysis using nonlinear mixed effects modeling. If data permit, estimates of population pharmacokinetic parameters such as CL/F as well as estimates of inter-individual and residual variability will be determined. In addition, effects of demographic or physiologic factors (eg, age, race, weight, gender, renal function) on pharmacokinetic parameters will be assessed. The results will be summarized in a separate report.

9.3. Safety Analysis

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this trial. The ASaT population consists of all randomized subjects who received at least one dose of investigational product. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data using the ASaT population. All safety analyses and summaries will be produced for the overall study population as well as for the China subpopulation.

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

To avoid the confounding influence of rescue therapy, the primary approach for most safety analyses will exclude data from the period following the initiation of rescue therapy. A secondary approach will include data following the initiation of rescue therapy. For serious AEs and discontinuations due to AEs, the approach that includes data following the initiation of rescue therapy will be considered primary.

Descriptive statistics will be used to summarize results and changes from baseline in clinical laboratory tests and in vital signs. The number and percentage of subjects with abnormal findings from ECGs will be tabulated by treatment group.

Furthermore, a 3-tier approach will be used to summarize AEs. Tier-1 AEs consist of pre-specified adverse events 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 will 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 are common, occurring in 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. The confidence intervals are for estimation purposes only. 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.

9.4. Data Monitoring Committee

This trial will use an external Data Monitoring Committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the trial according to the 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 E-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 communications between these organizations. The Sponsor will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, 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 CRFs is accurate. The Investigator and institution will allow Pfizer/Merck monitors/auditors 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 trial.

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 informed consent documents, 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 trial 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, informed consent documents, 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 informed consent document 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 trial 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. Subject Recruitment

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

12.5. 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

End of Trial is defined as last subject last visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this trial 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, Pfizer/Merck retains the right to discontinue development of ertugliflozin at any time.

If a trial 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

The Sponsor fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on http://www.clinicaltrials.gov/ (ClinicalTrials.gov). The Sponsor registers study protocols and posts Basic Results on ClincialTrials.gov for Sponsor interventional studies in human subjects that evaluate the safety and/or efficacy of ertugliflozin.

The results are posted in a tabular format called Basic Results.

For studies involving ertugliflozin, the timing of the posting depends on whether ertugliflozin is approved for marketing in any country at the time the trial is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, the Sponsor posts results within one year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, the Sponsor posts results one year from last subject, last visit (LSLV).

- For studies involving products that are not yet approved in any country, the Sponsor posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US).

- For studies involving products whose drug development is discontinued before approval, the Sponsor posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

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 trial concluded according to the pre-specified protocol or was terminated.

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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