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| Official Protocol Title: | A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study With A 78-Week Extension To Evaluate The Efficacy And Safety Of Ertugliflozin In Subjects With Type 2 Diabetes Mellitus And Inadequate Glycemic Control On Metformin Monotherapy |
| NCT number: | NCT02033889 |
| Document Date: | 20-Sep-2013 |



CLINICAL PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 26-WEEK MULTICENTER STUDY WITH A 78-WEEK EXTENSION TO EVALUATE THE EFFICACY AND SAFETY OF ERTUGLIFLOZIN IN SUBJECTS WITH TYPE 2 DIABETES MELLITUS AND INADEQUATE GLYCEMIC CONTROL ON METFORMIN MONOTHERAPY

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|--|---|
| Compound: | MK-8835/PF-04971729 |
| Compound Name: | Ertugliflozin |
| United States (US) Investigational New Drug (IND) Number: | 106,447 |
| European Clinical Trial Database (EudraCT) Number: | 2013-003290-95 |
| Protocol Number: | MK-8835-007-00 (Merck Protocol Number) B1521017 (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.

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Document History

| Document | Version Date | Summary of Changes |
|-------------------|-------------------|----------------------|
| Original protocol | 20 September 2013 | Not Applicable (N/A) |

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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 subjects with T2DM who have inadequate glycemic control on metformin monotherapy. This trial will also provide an assessment of bone safety of ertugliflozin by measurement of bone mineral density (BMD).

Objectives and Hypotheses:

In subjects with T2DM and inadequate glycemic control on a stable dose of metformin monotherapy;

The primary objectives and hypotheses of the trial are:

1. **Objective:** At Week 26, to assess the effect on HbA1c of 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in HbA1c for 15 mg ertugliflozin is greater than that for placebo.

2. **Objective:** At Week 26, to assess the effect on HbA1c of 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, 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:

1. **Objective:** At Week 26, to assess the effect on fasting plasma glucose (FPG) of 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in FPG for 15 mg ertugliflozin is greater than that for placebo.

2. **Objective:** At Week 26, to assess the effect on FPG of 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in FPG for 5 mg ertugliflozin is greater than that for placebo.

3. **Objective:** At Week 26, to assess the effect on body weight of 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in body weight for 15 mg ertugliflozin is greater than that for placebo.

4. **Objective:** At Week 26, to assess the effect on body weight of 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in body weight for 5 mg ertugliflozin is greater than that for placebo.

5. **Objective:** At Week 26, to assess the proportion of subjects with an HbA1c <7% (53 mmol/mol) treated with 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the proportion of subjects with an HbA1c <7% (53 mmol/mol) treated with 15 mg ertugliflozin is greater than that for placebo.

6. **Objective:** At Week 26, to assess the proportion of subjects with an HbA1c <7% (53 mmol/mol) treated with 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the proportion of subjects with an HbA1c <7% (53 mmol/mol) treated with 5 mg ertugliflozin is greater than that for placebo.

7. **Objective:** At Week 26, to assess the effect on systolic blood pressure of 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in systolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

8. **Objective:** At Week 26, to assess the effect on systolic blood pressure of 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in systolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

9. **Objective:** At Week 26, to assess the effect on diastolic blood pressure of 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in diastolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

10. **Objective:** At Week 26, to assess the effect on diastolic blood pressure of 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in diastolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

11. **Objective:** At Week 26, to assess the proportion of subjects with an HbA1c $\leq 6.5\%$, incidence of subjects requiring glycemic rescue therapy, and time to initiation of glycemic rescue therapy for each ertugliflozin arm compared with placebo.
12. **Objective:** At Week 52, to assess the change from baseline in efficacy endpoints relating to HbA1c and FPG; proportion of subjects with an HbA1c $< 7\%$; the proportion of subjects with an HbA1c $\leq 6.5\%$; incidence of subjects requiring glycemic rescue therapy; and time to initiation of glycemic rescue therapy for each of the two ertugliflozin arms.
13. **Objective:** At Week 52, to assess the change from baseline in efficacy endpoints relating to body weight, and the change from baseline in systolic and diastolic blood pressure.
14. **Objective:** At Week 104, to assess the change from baseline in efficacy endpoints relating to HbA1c, and FPG; proportion of subjects with an HbA1c $< 7\%$; proportion of subjects with an HbA1c $\leq 6.5\%$, incidence of subjects requiring glycemic rescue therapy; and time to initiation of glycemic rescue therapy for each of the two ertugliflozin arms.
15. **Objective:** At Week 104, to assess the change from baseline in efficacy endpoints relating to body weight, and the change from baseline in systolic and diastolic blood pressure.
16. **Objective:** To descriptively summarize pharmacokinetics of ertugliflozin in this study and provide pharmacokinetic (PK) data for potential population PK analysis.

Secondary objectives related to bone safety are:

17. **Objective:** At Week 26, to assess the effect on BMD as measured by dual energy X-Ray Absorptiometry (DXA) at the lumbar spine (L₁-L₄), femoral neck, total hip, and distal forearm for each of the two ertugliflozin arms ertugliflozin as compared with placebo.
18. **Objective:** At Week 26, to assess the effect on bone biomarkers of each of the two doses of ertugliflozin as compared with placebo.
19. **Objective:** At Week 52, to assess the change from baseline in BMD as measured by DXA at the lumbar spine (L₁-L₄), femoral neck, total hip and distal forearm for each of the two ertugliflozin arms.
20. **Objective:** At Week 52, to assess the change from baseline in bone biomarkers for each of the two ertugliflozin arms.

21. **Objective:** At Week 104, to assess the change from baseline in BMD as measured by DXA at the lumbar spine (L₁-L₄), femoral neck, total hip and distal forearm for each of the two ertugliflozin arms.
22. **Objective:** At Week 104, to assess the change from baseline in bone biomarkers for each of the two ertugliflozin arms.

Study Population:

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 dose ≥1500 mg/day.

Approximately 50% of the population enrolled in the trial will be women who have been post-menopausal for 3 years or more (at least 3 years since their last menstrual period [LMP] or bilateral oophorectomy performed 3 years or more prior to screening), and the randomization will be stratified based on this post-menopausal status (as well as geographical region – primarily to facilitate drug supply logistics). Details on the stratification factors for randomization are provided in [Section 4.3](#).

Study Design:

This trial is a Phase 3 multi-center, randomized, parallel-group study with a 26-week, double-blind, placebo-controlled treatment period (Phase A) followed by a 78-week double-blind, extension period (Phase B) in subjects with T2DM and inadequate glycemic control on metformin monotherapy. Subjects could participate in the trial for approximately up to 119 weeks. The trial includes a 1-week screening period, a variable interval for metformin titration (if needed), and at least an 8-week metformin stable dose period when subjects will discontinue and remain off any previous allowable background diabetes therapy (except for metformin), and a 2-week single-blind placebo run-in period 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 washoff of another 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 oral AHAs: sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, meglitinide, or alpha-glucosidase inhibitor.

Subjects receiving metformin in combination with another allowable AHA must discontinue the other AHA beginning at the Screening Visit 2 (S2) and remain off the other AHA for the duration of this trial.

The following table provides information on the allowable 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

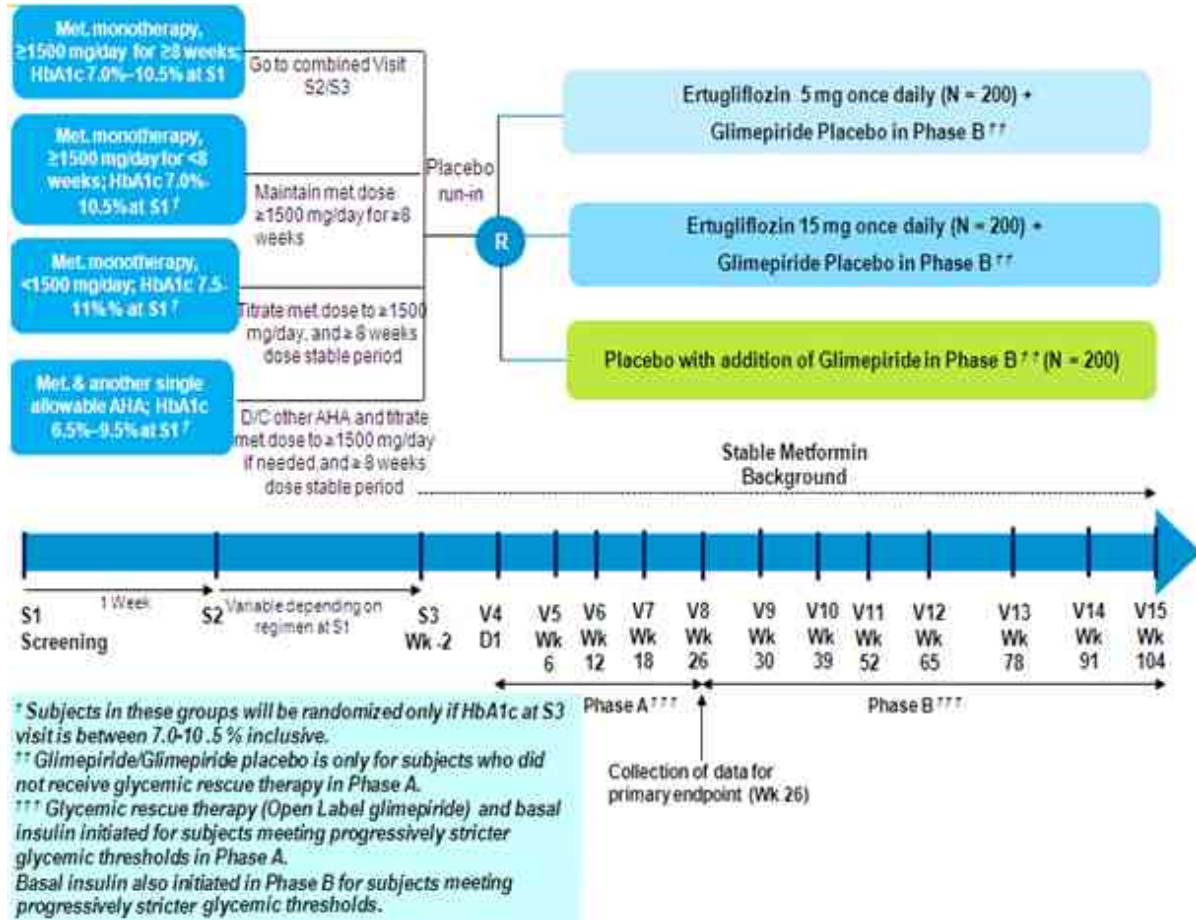
| Diabetes Therapy at Screening Visit (S1) | HbA1c Inclusion Criterion at S1 | Change in Background Diabetes Therapy Prior to Placebo Run-in (S3) |
|--|--|---|
| Metformin monotherapy, ≥ 1500 mg/day for ≥ 8 weeks | 7.0%–10.5% (53-91 mmol/mol), inclusive | None. Subjects proceed directly to a combined S2/S3 Visit. |
| 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 other 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.

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The trial scheme is illustrated below:



Met= Metformin

The trial is designed with three phases:

- Screening phase including discontinuation of background diabetes therapy other than metformin (if applicable) and a 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.
- Phase A: Randomized, double-blind, placebo-controlled treatment period (Visits V4 through V8)** - a 26-week treatment period for assessment of primary and secondary safety and efficacy endpoints. At entry into Phase A, subjects will be randomized to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo, while maintaining metformin at a dose ≥ 1500 mg/day. Glycemic rescue therapy with open-label glimepiride and basal insulin should be initiated in subjects with glucose values exceeding protocol-specified

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values as mentioned in [Section 5.6](#). Dosing and titration of open-label glimepiride rescue therapy is at the discretion of the Investigator.

3. **Phase B: Double-Blind, extension period (Visits V8 through V15)** – a 78-week, double-blind extension period where subjects randomized to ertugliflozin will remain on their randomized treatment–: subjects randomized to placebo will have the addition of treatment with glimepiride (if they were not rescued during Phase A), maintaining the double-blinding; this is accomplished by the use of *blinded glimepiride or matching placebo*, as described below:

- Subjects randomized to ertugliflozin (5 or 15 mg) are continued on their randomized dose of ertugliflozin, *and*
 - If not rescued in Phase A: *will be started* on the addition of placebo matching glimepiride (and with mock uptitration using glimepiride placebo tablets matching 1 or 2 mg tablets, as determined appropriate by the investigator).
 - If rescued in Phase A: *will not be started* on placebo matching glimepiride, and open-label glimepiride will be continued into Phase B.
- Subjects randomized to the placebo treatment group will continue on the placebo tablets matching ertugliflozin *and*
 - If not rescued in Phase A: will be started on the addition of glimepiride (1 mg), with titration with 1 or 2 mg tablets (to maximum allowed dose [6 or 8 mg] based upon the local label]) as determined appropriate by the investigator.
 - If rescued in Phase A: *will not be started* on glimepiride, and open label rescue glimepiride will be continued into Phase B.

Note: subjects whose Week 26 visit fasting fingerstick glucose is <110 mg/dL (6.1 mmol/L) will **not** have the glimepiride or matching placebo initiated at the Week 26 visit. At each subsequent scheduled study visit, if the fasting fingerstick glucose (FFSG) is \geq 110 mg/dL, glimepiride or matching placebo tablets may be initiated (unless not considered appropriate by the investigator based upon the risk of hypoglycemia).

During Phase B, glycemic rescue therapy with basal insulin should be initiated in subjects with glucose values or HbA1c values exceed protocol-specified values (See [Section 5.6](#))

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 adult subjects with T2DM and inadequate glycemic control on metformin monotherapy. It is also designed to evaluate the longer-term efficacy, safety and tolerability of ertugliflozin during the entire 104-week treatment period, which includes a 78-week double-blind extension period. A key purpose of this 78-week extension period is

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to collect additional safety data of ertugliflozin on BMD. The effect of ertugliflozin on BMD will be assessed by DXA. All DXA data throughout the trial will be forwarded to a central evaluation facility to ensure standardization.

Approximately 600 subjects will be randomized to ensure a minimum of 480 subjects (160 per arm) will provide HbA1c data at the Week 26 primary timepoint. Given the plans not to replace those subjects who are withdrawn early, the 600 subjects randomized will also account for an approximate 20% premature withdrawal rate for HbA1c data to allow for withdrawn subjects who will still be included in the analysis, but will not necessarily have Week 26 data available.

Glycemic Rescue Therapy:

Subjects will be prescribed rescue therapy in the form of open-label glimepiride and basal insulin, and dosed according to Investigator judgment, if they meet specific glycemic criteria which become progressively more stringent throughout the trial. Provision of rescue with basal insulin is to occur only once subjects have first been titrated to a maximum tolerated or maximum approved dose of glimepiride (based on local country label) and continue to exceed the protocol-specified glycemic values.

Endpoints:

Primary Endpoint:

- The primary endpoint is the change in HbA1c from Baseline at Week 26.

Secondary Endpoints:

- Change in FPG from Baseline to Week 26.
- Change in body weight from Baseline to Week 26.
- Incidence of HbA1c of <7% (53 mmol/mol) at Week 26.
- Change in systolic and diastolic blood pressure from Baseline to Week 26.
- Change in HbA1c, FPG, and body weight from Baseline to Weeks 52 and 104.
- Incidence of HbA1c <7% (53 mmol/mol) at Weeks 52 and 104.
- Incidence of HbA1c ≤6.5% (48 mmol/mol) at Weeks 26, 52 and 104.
- Change in systolic and diastolic blood pressure from Baseline to Weeks 52 and 104.
- Incidence of subjects requiring glycemic rescue therapy up to Weeks 26, 52 and 104.
- Time to glycemic rescue therapy up to Weeks 26, 52 and 104.

- Endpoints related to pharmacokinetics of ertugliflozin.

Secondary endpoints related to bone safety are:

- Change in BMD as measured by DXA at the lumbar spine (L₁-L₄), femoral neck, total hip and distal forearm from Baseline to Week 26.
- Change in BMD as measured by DXA at the lumbar spine (L₁-L₄), femoral neck, total hip and distal forearm from Baseline to Weeks 52 and 104.
- Change from baseline in bone biomarkers at Weeks 26, 52 and 104.

Statistical Methods:

Sample Size: With respect to the primary endpoint of reduction in HbA1c from Baseline to Week 26 and assuming a standard deviation (SD) of 1.0%, the sample size of approximately 600 subjects (200 per arm) provides at least 99% power to detect a difference of 0.5% between each ertugliflozin dose and placebo (and 98% power for detecting this difference for both doses vs placebo) using a two-sided 0.05 alpha level test, allowing for a dropout rate of up to 20%. To control the overall Type I error rate at 0.05 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.

The sample size for this trial also provides adequate precision for the comparison of ertugliflozin versus placebo with respect to the changes in BMD from Baseline to Week 26. In a recent study of another SGLT2 inhibitor (dapagliflozin) in subjects with inadequately controlled T2DM on metformin, the largest variability for the change from baseline in BMD was at the total hip site, with an SD of approximately 3.3% after 50 weeks.¹³ Assuming that the SD of the change in BMD increases over time, 3.3% was taken as a conservative estimate of the variability at 26 weeks for precision calculations, and also to ensure adequate precision for all BMD sites.

Assuming an SD of 3.3% and allowing for a dropout rate of up to 15% at Week 26, the half-width of the 95% confidence interval for the between-treatment difference is expected to be $\pm 0.7\%$ from the point estimate for the overall study population, and also of approximately $\pm 1.0\%$ for the ≥ 3 years post-menopausal sub-group which will be analyzed separately (approximately 50% of the overall study population).

These CI half-widths would be precise enough to rule out clinically relevant changes in BMD, both for the overall study population and the ≥ 3 years post-menopausal subgroup. This is based on changes in BMD that are approximately 50% of the average changes from baseline to Week 80 observed for thiazolidinediones, which are known to be associated with significant bone loss and an increased risk of fracture.¹⁹

BMD data will not be censored at the point of a subject taking glycemic rescue therapy so the dropout rate assumed for this precision calculation (15%) is lower than that assumed for the

HbA1c power calculation (20%). However BMD data will be censored at the point of a subject taking BMD rescue therapy.

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 Phase A of the trial, including Baseline and post-Baseline time points. The post glycemic rescue therapy data from subjects who require rescue therapy prior to Week 26 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 treatment, visit, treatment by-visit interaction and menopausal status randomization stratum. 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. 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.

Analysis of Secondary Endpoints:

The proportion of subjects with an HbA1c <7% (53 mmol/mol) at Week 26 will be analyzed using a logistic regression model with terms for treatment (categorical) and Baseline HbA1c (continuous). Summary measures from the analysis will include the odds ratio, 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.

The secondary efficacy endpoints of FPG, proportion of subjects achieving an HbA1c <7%, 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.

Analysis of BMD

The changes in BMD from Baseline to Week 26 at the lumbar spine, femoral neck, total hip, and distal forearm will be safety endpoints. A BMD analysis set will be defined to include

all randomized subjects who have received at least one dose of investigational product and have at least one observation of BMD at any time during Phase A of the trial, including Baseline and post-Baseline time points. For analyses of changes in BMD, measurements obtained post glycemic rescue therapy will be utilized if available; however BMD measurements will be censored at the point of a subject taking BMD rescue therapy.

Changes from Baseline to Week 26 in BMD will be analyzed by fitting a constrained longitudinal data analysis model with terms for treatment, visit, treatment by-visit interaction and menopausal status randomization stratum. Least-squares means and 95% confidence intervals will be used to estimate the treatment effect (difference between ertugliflozin and placebo) at Week 26.

The BMD analyses will also be conducted separately for the male and female subgroups, and also for subjects who completed ≥ 20 weeks of study treatment. Another sub-group analysis will be conducted separately for women post-menopausal for 3 years or more after last LMP (approximately 50% of the overall study population). Descriptive statistics will also be provided for each of the four randomization strata.

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 | V9 | V10 | V11 | V12 | V13 | V14 | V15 | | | |
|--|-----|-----------------|---------|--------------------|---------|---------|---------|---------|---------|----------|----------|----------|----------|----------|---------------------------|----------------------------------|---------------------------|---|
| Study Day or Week ^b | N/A | N/A | Day -14 | Day 1 ^c | Wk 6 | Wk 12 | Wk 18 | Wk 26 | Wk 30 | Wk 39 | Wk 52 | Wk 65 | Wk 78 | Wk 91 | Wk 104 or ET ^d | 2 Wk f/u phone call ^e | Rescue Visit ^f | |
| Visit Window | | | | ±5 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±14 days | ±14 days | ±14 days | ±14 days | ±14 days | ±14 days | ±14 days | ±3 days | |
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Contact IVRS System | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Informed Consent for Future Biomedical Research | 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 | | | | X | | | X |
| Body Weight (measured in | X | | X | X | X | X | X | X | | X | X | X | X | X | X | | | X |

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| Protocol Activity | S1 | S2 ^a | S3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 | V14 | V15 | | |
|--|-----|-----------------|---------|--------------------|---------|---------|---------|---------|---------|----------|----------|----------|----------|----------|---------------------------|----------------------------------|---------------------------|
| Study Day or Week ^b | N/A | N/A | Day -14 | Day 1 ^c | Wk 6 | Wk 12 | Wk 18 | Wk 26 | Wk 30 | Wk 39 | Wk 52 | Wk 65 | Wk 78 | Wk 91 | Wk 104 or ET ^d | 2 Wk f/u phone call ^e | Rescue Visit ^f |
| Visit Window | | | | ±5 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±14 days | ±14 days | ±14 days | ±14 days | ±14 days | ±14 days | ±3 days | |
| duplicate) | | | | | | | | | | | | | | | | | |
| Sitting blood pressure/pulse rate ^h | X | | | X | X | X | X | X | | X | X | X | X | X | X | | X |
| Postural (orthostatic) Blood Pressure/Pulse Rate ⁱ | | | X | X | X | | | X | | | | | | | | | X ⁱ |
| 12-Lead ECG ^j | | X | | X | | | | X | | | X | | | | X | | |
| DXA ^k | | | X | | | | | X | | | X | | | | X | | |
| Laboratory | | | | | | | | | | | | | | | | | |
| Fasting Safety Lab Tests (chemistry, hematology) | X | | | X | | X | | X | | | X | | X | | X | | X |
| Fasting Safety Lab Tests (chemistry) | | | | | X | | X | | | X | | X | | X | | | |
| Routine Urinalysis ^{l,m} | X | | | X | | | | X | | | X | | X | | X | | X |
| Urinary Albumin/Creatinine Ratio ^m | | | | X | | | | X | | | X | | | | X | | |
| Site fingerstick HbA1c ⁿ | X | | | | | | | | | | | | | | | | |
| Fasting Fingerstick Glucose in Clinic | | X | X | | | | | X | X | X | X | X | X | X | X | | |
| Fasting C-peptide ^o | X | | | | | | | | | | | | | | | | |
| Fasting Triglycerides/TSH/PTH | X | | | | | | | | | | | | | | | | |
| Lipid Panel and Apolipoproteins ^p | | | | X | | X | | X | | | X | | | | X | | X |
| Pregnancy Test (women of childbearing potential only) ^q | X | | X | X | X | X | X | X | | X | X | X | X | X | X | | |

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| Protocol Activity | S1 | S2 ^a | S3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 | V14 | V15 | | |
|--|-----|-----------------|----------------|--------------------|---------|---------|---------|---------|---------|----------|----------|----------|----------|----------|---------------------------|----------------------------------|---------------------------|
| Study Day or Week ^b | N/A | N/A | Day -14 | Day 1 ^c | Wk 6 | Wk 12 | Wk 18 | Wk 26 | Wk 30 | Wk 39 | Wk 52 | Wk 65 | Wk 78 | Wk 91 | Wk 104 or ET ^d | 2 Wk f/u phone call ^e | Rescue Visit ^f |
| Visit Window | | | | ±5 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±14 days | ±14 days | ±14 days | ±14 days | ±14 days | ±14 days | ±3 days | |
| HbA1c | X | | X ^f | X | X | X | X | X | | X | X | X | X | X | X ^g | | X ^g |
| Fasting Plasma Glucose | X | | | X | X | X | X | X | | X | X | X | X | X | X | | X |
| PK Sample for ertugliflozin ^h | | | | | X | X | X | | X | | | | | | | | |
| Whole Blood (DNA) for Future Biomedical Research ^h | | | | X | | | | | | | | | | | | | |
| Plasma for Future Biomedical Research ^h | | | | X | | | | X | | | | | | | X | | X |
| Serum for Future Biomedical Research ^h | | | | X | | | | X | | | | | | | X | | X |
| CTX, PINP, PTH ^v | | | | X | | | | X | | | X | | | | X | | |
| 25-hydroxyvitamin D | | | X | | | | | | | | | | | | | | |
| Drug | | | | | | | | | | | | | | | | | |
| Dispense Single-Blind Placebo Run-in | | | X | | | | | | | | | | | | | | |
| Dispense Double-Blind ertugliflozin/placebo | | | | X | X | X | X | X | | X | X | X | X | X | | | |
| Dispense Blinded glimepiride/placebo for non-rescued subjects OR continued Open-Label Glimpiride for subjects rescued in Phase A | | | | | | | | X | X | X | X | X | X | X | | | |
| Witnessed dose of Investigational Product in Clinic | | | X | X | | | | X | | | | | | | | | |
| Dispense glycemic rescue medication as appropriate | | | | | X | X | X | X | | X | X | X | X | X | | | X |

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| Protocol Activity | S1 | S2 ^a | S3 | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 | V14 | V15 | | |
|--|-----|-----------------|---------|--------------------|---------|---------|---------|---------|---------|----------|----------|----------|----------|----------|---------------------------|----------------------------------|---------------------------|
| Study Day or Week ^b | N/A | N/A | Day -14 | Day 1 ^c | Wk 6 | Wk 12 | Wk 18 | Wk 26 | Wk 30 | Wk 39 | Wk 52 | Wk 65 | Wk 78 | Wk 91 | Wk 104 or ET ^d | 2 Wk f/u phone call ^e | Rescue Visit ^f |
| Visit Window | | | | ±5 days | ±7 days | ±7 days | ±7 days | ±7 days | ±7 days | ±14 days | ±14 days | ±14 days | ±14 days | ±14 days | ±14 days | ±3 days | |
| Assess Compliance | | | | X | X | X | X | X | | X | X | X | X | X | X | | X |
| Prior/Concomitant medication review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Subject Education / Monitoring | | | | | | | | | | | | | | | | | |
| Diet and Exercise Counseling (S2)/Monitoring ^w | | X | X | X | X | X | X | X | | X | X | X | X | X | X | | X |
| Distribute glucose meter (S2) and glucose meter supplies | | X | X | X | X | X | X | 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 ^x | | X | | | | | | | | | | | | | | | |
| Review/dispense Hypoglycemia Assessment and Self-Monitoring Blood Glucose logs | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Adverse Event Monitoring ^y | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

- 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 AHA therapy at the S2 visit). These subjects must remain on 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 metformin monotherapy ≥1500 mg/day for at least 8 weeks at S1, will have a combined S2/S3 visit.
- Day 1 has a recommended visit window of ±5 days relative to S3 (or combined S2/S3 visit); Weeks 6, 12, 18, 26, 30 have a recommended visit window of ±7 days relative to Day 1; Visits from Week 39 through 104 have a recommended visit window of ±14 days relative to Day 1; 2 week follow-up phone call is recommended to be completed within a ±3-day window.

- 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 7.8](#), if applicable. See [Section 6.7](#) 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 7.8](#), if applicable.
- f. Subjects who require glycemic rescue therapy per [Section 5.6](#) must have 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, extremities and skin.
- 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](#). Postural changes should only be collected at the Rescue Visit if the Rescue Visit occurs in Phase A.
- j. S2 ECG is read locally at investigative site. ECG for all other time points should be submitted to be read centrally.
- k. Screening DXA scans should be performed at Visit S3 or at least ten days before Day 1 visit. In case of discontinuation of investigational product during Phase A, a DXA scan will be performed if the discontinuation occurs between Week 12 and Week 26. In case of discontinuation of investigational product during Phase B, a DXA scan will be performed if the discontinuation occurs at least 12 weeks from the previous scan. See [Section 7.6](#) for additional details.
- l. Routinely collected urinalysis samples will be sent to the central laboratory for dipstick analysis (not including glucose assessment) and microscopy if dipstick is positive for blood, nitrites, leukocytes and/or protein.
- m. 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.
- n. Site fingerstick HbA1c is not mandatory, but may be used, at the discretion of the Investigator, for screening subjects. However, a fingerstick HbA1c cannot substitute for a central laboratory measured HbA1c to determine if a subject meets entry criteria.
- o. C-peptide test is only for subjects assessed by the Investigator as possibly having type 1 diabetes.
- p. Includes total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides at all time points noted above. ApoB and ApoA-1 are included at Day 1 and Week 26 visits as well as the glycemic rescue visit and early termination visit.
- q. 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.
- r. 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 AHA therapy at S2) must have an HbA1c of 7.0-10.5% (53-91 mmol/mol) at S3 in order to be randomized.
- s. HbA1c should not be obtained if ET or rescue visit occurs within 6 weeks of randomization.
- t. 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).

- u. The Future Biomedical Research (FBR) informed consent must be obtained before FBR samples are drawn. The FBR sample for DNA analysis should be obtained pre-dose, at Day 1/Visit 4, as the last sample drawn, on subjects who qualify for randomization, but may be obtained at a later date during the trial after the FBR informed consent is obtained. The plasma and serum samples for FBR should be collected at Day 1 (pre-dose), Week 26, Week 104 or Early Termination Visit, and Rescue Visit (if applicable). The plasma and serum samples for FBR should be collected at all time points, even if the pre-dose or other time point was not collected.
- v. The sample(s) for measurement of bone biomarkers and PTH should not be collected if the investigational product has been discontinued for >7 days prior to the collection of the sample(s).
- w. Subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at S2 Visit 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.
- x. Subjects should be educated on the symptoms of hyperglycemia (eg, polyuria, polydipsia) at S2.
- y. Assess AEs, SAEs, hypoglycemia assessment log as well as potential clinical events for adjudication (See [Sections 7.4.6, 7.8, 8](#) for additional detail).

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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 |
| Apo A1 | apolipoprotein A1 |
| ApoB | apolipoprotein B |
| AST | aspartate transaminase |
| AUC | area under the concentration-time curve |
| BMD | bone mineral density |
| BMI | body mass index |
| 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 |
| CTX | carboxy-terminal cross-linking telopeptides of Type I collagen |
| CV | cardiovascular |
| DNA | deoxyribonucleic acid |
| DPP-4 | dipeptidyl peptidase-4 |
| DXA | dual energy X-Ray Absorptiometry |
| ECG | electrocardiogram |
| ECI | event of clinical interest |

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| | |
|------------------|---|
| ED ₅₀ | dose achieving 50% of maximum response |
| EEA | European Economic Area |
| eGFR | estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| ER | Extended Release |
| ET | early termination of the study |
| FAC | Fracture Adjudication Committee |
| FDA | Food and Drug Administration |
| FBR | Future Biomedical Research |
| 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 |
| iPTH | intact parathyroid hormone |
| IR | Immediate Release |
| IRB | institutional review board |
| IUD | Intra-uterine device |
| IVRS | interactive voice response system |
| LDL-C | low density lipoprotein cholesterol |
| LMP | last menstruation period |
| MACE | major adverse cardiovascular events |
| MDRD | Modification of Diet in Renal Disease |
| N/A | Not applicable |
| NASH | Non-alcoholic steatohepatitis |
| NOAEL | no observed adverse effect level |

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| | |
|-------------|--|
| NPH | Neutral protamine Hagedorn |
| NYHA | New York Heart Association |
| P1NP | procollagen type I N-terminal propeptide |
| PK | pharmacokinetic(s) |
| PR interval | time from the beginning of the P wave to the end of the QRS complex on electrocardiogram |
| PTH | parathyroid hormone |
| 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 |
| RNA | ribonucleic acid |
| 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 |
| SERM | Selective Estrogen Receptor Modulators |
| SGLT1 | Sodium Glucose co-Transporter 1 |
| SGLT2 | Sodium Glucose co-Transporter 2 |
| SLC5A | Sodium Glucose co-Transporter gene family |
| SOA | schedule of activity |
| SRSD | single reference safety document |
| SUSAR | suspected unexpected serious adverse reactions |
| T2DM | type 2 diabetes mellitus |
| TIA | Transient ischemic attack |
| TSH | thyroid-stimulating hormone |

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Ertugliflozin (MK-8835/PF-04971729)

MK-8835-007-00/B1521017

Final Protocol, 20 September 2013

| | |
|-----|---------------------------|
| UGE | urinary glucose excretion |
| US | United States |
| UTI | urinary tract infections |

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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 T2DM also represents one of the largest medical burdens in the United States resulting in direct medical costs of \$176 billion and \$69 billion in loss of productivity in 2012.² At present, it is estimated that 25.8 million people in the US have diabetes (8.3% of the population) of which 7 million remain undiagnosed.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 Orally administered pharmacological agents that lower glucose while also reducing other risk factors, eg, by lowering body weight and reducing blood pressure, represent a major advantage in the treatment of diabetes.

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 subjects with T2DM and 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.

In addition, this study will assess changes in bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA), and so provide important information on the bone safety of ertugliflozin.

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 August 2013, one SGLT2 inhibitor is approved in the U.S. (canagliflozin) and another (dapagliflozin) is approved in 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. As of August 2013, a total of 479 subjects have 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 August 2013, there have been no deaths, and a total of 11 Serious Adverse Events (SAEs) were reported in 9 subjects. Across the program, a total of 10 subjects (1.5%) were withdrawn due to adverse events (AEs). The most frequent AEs reported with ertugliflozin use in the Phase 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 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. Small mean increases in serum calcium, serum phosphate and serum magnesium, and intact parathyroid hormone (iPTH) all within the laboratory reference range,

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were observed following 12 weeks of dosing with ertugliflozin. There was a suggestion of changes in markers of bone resorption, though there did not appear to be a clear dose-dependent effect with increasing dose of ertugliflozin. In totality, the clinical relevance of these findings remains unclear. However, the effect of ertugliflozin on BMD will be evaluated in this trial, and all clinical fractures will be adjudicated throughout the Phase 3 program by an independent committee and will be included in a pooled analysis.

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

Phase 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.¹¹ 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 (PF-04971729).

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 subjects who have inadequate glycemic control on metformin monotherapy at or near maximally effective doses (ie, ≥ 1500 mg per day). Subjects already on metformin monotherapy at protocol-specified doses (≥ 1500 mg per day) for at least 8 weeks at Screening Visit 1 and who meet other enrollment criteria, will go directly from Screening Visit 1 to Screening Visit 3 to enter the 2-week single-blind placebo run-in period.

In addition to subjects with inadequate control on metformin monotherapy at protocol-specified doses, a broader range of subjects will be screened for the study, including subjects on metformin in combination with another allowable single AHA agent, or metformin at a dose below the protocol-specified dose (ie, < 1500 mg per day). Other potentially eligible subjects, not yet on metformin monotherapy at protocol-specified doses, will be switched at Screening Visit 2 to a regimen of metformin monotherapy and need to attain a dose of ≥ 1500 mg per day and then enter a dose stable period, including at least 8 weeks on a stable dose of metformin monotherapy prior to Screening Visit 3, where they

will enter a 2 week single-blind placebo run-in period. These subjects will have HbA1c measured again at Screening Visit 3 to determine if they qualify for enrollment.

Beyond the effects of ertugliflozin mentioned above on electrolytes and bone biomarkers from Phase 2, a small decrease in BMD, of unclear significance, was observed in a clinical trial of one agent in the SGLT2 class (canagliflozin), but not in another (dapagliflozin). SGLT2-induced urinary caloric loss produces body weight loss, which may potentially reduce BMD.¹⁸ Based upon these observations, this trial will assess the effect of ertugliflozin on BMD, and also obtain data on the effect of ertugliflozin on bone biomarkers.

Approximately 50% of the population enrolled in the trial will be women who have been post-menopausal for 3 years or more (at least 3 years since their last menstrual period [LMP] or bilateral oophorectomy performed 3 years or more prior to screening), and the randomization will be stratified based on this post-menopausal status (as well as geographical region – primarily to facilitate drug supply logistics). Details on the stratification factors for randomization are provided in [Section 4.3](#).

The population to be enrolled in this study represents subjects appropriate to assess the primary and secondary objectives in the study. Collecting BMD data with this mechanism is important in subjects with T2DM regardless of age or sex, and particularly important in a population of post-menopausal women. Subjects with a lumbar spine, femoral neck, total hip or distal forearm regions BMD T-score of less than -2.5 as measured at Screening will be excluded given that this trial prohibits the use of concomitant bone-active medications such as bisphosphonates, which would likely be used by such a population. Subjects receiving other medications affecting bone turnover, such as estrogen receptor modulators, are also excluded from this trial as potentially these medications may confound the interpretation of any potential effect of ertugliflozin on BMD. Due to concerns regarding the quality of bone imaging, subjects with a BMI >40.0 kg/m² will be excluded from this trial.

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% |

ED₅₀= dose achieving 50% of maximum response

UGE= urinary glucose excretion

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In addition, the dose-response modeling of 24-hour urinary glucose excretion (UGE) in healthy volunteers estimated the ED₅₀ 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). Thus, both the 5 and 15 mg doses are expected to provide clinically meaningful efficacy and allow for a thorough assessment of the benefit/risk of ertugliflozin in the Phase 3 program.

1.5.2. Rationale for Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on whole blood deoxyribonucleic acid (DNA), plasma and serum specimens collected during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling [ribonucleic acid (RNA)], proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes. Specimens may be used for future assay development. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetics (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs, and/or to ensure that subjects receive the correct dose of the correct drug at the correct time. The details of this Future Biomedical Research sub-trial are presented in [Appendix 1](#) Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in [Appendix 2](#).

2. STUDY OBJECTIVES, HYPOTHESES AND ENDPOINTS

2.1. Objectives and Hypotheses

In subjects with T2DM and inadequate glycemic control, on a stable dose of metformin monotherapy, the following are primary objectives and hypotheses of the trial:

1. **Objective:** At Week 26, to assess the effect on HbA1c of 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in HbA1c for 15 mg ertugliflozin is greater than that for placebo.

2. **Objective:** At Week 26, to assess the effect on HbA1c of 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, 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:

1. **Objective:** At Week 26, to assess the effect on fasting plasma glucose (FPG) of 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in FPG for 15 mg ertugliflozin is greater than that for placebo.

2. **Objective:** At Week 26, to assess the effect on FPG of 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in FPG for 5 mg ertugliflozin is greater than that for placebo.

3. **Objective:** At Week 26, to assess the effect on body weight of 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in body weight for 15 mg ertugliflozin is greater than that for placebo.

4. **Objective:** At Week 26, to assess the effect on body weight of 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in body weight for 5 mg ertugliflozin is greater than that for placebo.

5. **Objective:** At Week 26, to assess the proportion of subjects with an HbA1c <7% (53 mmol/mol) treated with 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the proportion of subjects with an HbA1c <7% (53 mmol/mol) treated with 15 mg ertugliflozin is greater than that for placebo.

6. **Objective:** At Week 26, to assess the proportion of subjects with an HbA1c <7% (53 mmol/mol) treated with 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the proportion of subjects with an HbA1c <7% (53 mmol/mol) treated with 5 mg ertugliflozin is greater than that for placebo.

7. **Objective:** At Week 26, to assess the effect on systolic blood pressure of 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in systolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

8. **Objective:** At Week 26, to assess the effect on systolic blood pressure of 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in systolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

9. **Objective:** At Week 26, to assess the effect on diastolic blood pressure of 15 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in diastolic blood pressure for 15 mg ertugliflozin is greater than that for placebo.

10. **Objective:** At Week 26, to assess the effect on diastolic blood pressure of 5 mg ertugliflozin as compared with placebo.

Hypothesis: At Week 26, the mean reduction from baseline in diastolic blood pressure for 5 mg ertugliflozin is greater than that for placebo.

11. **Objective:** At Week 26, to assess the proportion of subjects with anHbA1c $\leq 6.5\%$, incidence of subjects requiring glycemic rescue therapy, and time to initiation of glycemic rescue therapy for each ertugliflozin arm compared with placebo.

12. **Objective:** At Week 52, to assess the change from baseline in efficacy endpoints relating to HbA1c, FPG; proportion of subjects with an HbA1c $< 7\%$; proportion of subjects with an HbA1c $\leq 6.5\%$; incidence of subjects requiring glycemic rescue therapy; and time to initiation of glycemic rescue therapy for each of the two ertugliflozin arms.

13. **Objective:** At Week 52, to assess the change from baseline in efficacy endpoints relating to body weight, and the change from baseline in systolic and diastolic blood pressure.

14. **Objective:** At Week 104, to assess the change from baseline in efficacy endpoints relating to HbA1c, FPG; proportion of subjects with anHbA1c $< 7\%$; proportion of subjects with anHbA1c $\leq 6.5\%$, incidence of subjects requiring glycemic rescue therapy; and time to initiation of glycemic rescue therapy for each of the two ertugliflozin arms.

15. **Objective:** At Week 104, to assess the change from baseline in efficacy endpoints relating to body weight, and the change from baseline in systolic and diastolic blood pressure.

16. **Objective:** To descriptively summarize pharmacokinetics of ertugliflozin in this study and provide PK data for potential population PK analysis.

Secondary objectives related to bone safety are:

17. **Objective:** At Week 26, to assess the effect on BMD as measured by DXA at the lumbar spine (L₁-L₄), femoral neck, total hip, and distal forearm for each of the two ertugliflozin arms ertugliflozin as compared with placebo.
18. **Objective:** At Week 26, to assess the effect on bone biomarkers of each of the two doses of ertugliflozin as compared with placebo.
19. **Objective:** At Week 52, to assess the change from baseline in BMD as measured by DXA at the lumbar spine (L₁-L₄), femoral neck, total hip and distal forearm for each of the two ertugliflozin arms.
20. **Objective:** At Week 52, to assess the change from baseline in bone biomarkers for each of the two ertugliflozin arms.
21. **Objective:** At Week 104, to assess the change from baseline in BMD as measured by DXA at the lumbar spine (L₁-L₄), femoral neck, total hip and distal forearm for each of the two ertugliflozin arms.
22. **Objective:** At Week 104, to assess the change from baseline in bone biomarkers for each of the two ertugliflozin arms.

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.
- Incidence of HbA1c of <7% (53 mmol/mol) at Week 26.
- Change in systolic and diastolic blood pressure from Baseline to Week 26.
- Change in HbA1c, FPG, and body weight from Baseline to Weeks 52 and 104.
- Incidence of HbA1c <7% (53 mmol/mol) at Weeks 52 and 104.
- Incidence of HbA1c ≤6.5% (48 mmol/mol) at Weeks 26, 52 and 104.
- Change in systolic and diastolic blood pressure from Baseline to Weeks 52 and 104.
- Proportion of subjects requiring glycemic rescue therapy up to Weeks 26, 52 and 104.

- Time to glycemic rescue therapy up to Weeks 26, 52 and 104.
- Endpoints related to pharmacokinetics of ertugliflozin.

Secondary endpoints related to bone safety are:

- Change in BMD as measured by DXA at the lumbar spine (L₁-L₄), femoral neck, total hip and distal forearm from Baseline to Week 26.
- Change in BMD as measured by DXA at the lumbar spine (L₁-L₄), femoral neck, total hip and distal forearm from Baseline to Weeks 52 and 104.
- Change from baseline in bone biomarkers at Weeks 26, 52 and 104.

As part of a large Phase 3 program for ertugliflozin, this protocol will contribute safety data to a program-wide meta-analysis of clinical cardiovascular events. Additional detail is provided in [Section 7.8.1](#).

To maintain the ability of the trial to provide information on long-term safety data, subjects who discontinue investigational product and do not withdraw consent will thereafter be contacted via telephone by the Investigator/qualified designee according to the same schedule as if the subject were still taking investigational product (ie, according to [Section the Schedule of Activities](#) and [Section 6](#)). Such subjects will be asked to return to the clinic at the time of the Week 104 visit. Additional details are provided in [Section 6.7](#).

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 (Phase A) followed by a 78-week double-blind, extension period (Phase B) in subjects with T2DM and inadequate glycemic control on metformin in monotherapy.

The trial includes a 1-week screening period, a variable interval for metformin titration (if needed), and at least an 8-week metformin stable dose period when subjects will discontinue and remain off any previous allowable background diabetes therapy (except for metformin), and a 2-week single-blind placebo run-in period prior to randomization. A follow-up phone call will take place 2 weeks after the last dose of investigational product. Subjects could participate in the trial for approximately up to 119 weeks.

The fixed, 2-week 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 include subjects taking a variety of baseline diabetes therapy regimens at the Screening visit by incorporating a period of metformin titration and dose stabilization, and washoff of another anti-hyperglycemic agent 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 oral anti-hyperglycemic agents (AHAs): sulfonylurea, DPP-4 inhibitor, meglitinide, or alpha-glucosidase inhibitor.

Subjects receiving metformin in combination with another allowable AHA must discontinue the other AHA beginning at the Screening Visit 2 (S2) and remain off the other AHA for the duration of this trial.

The following table provides information on the allowable 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 Screening Visit (S1) | HbA1c Inclusion Criterion at S1 | Change in Background Diabetes Therapy Prior to Placebo Run-in (S3) |
|--|--|--|
| Metformin monotherapy, ≥ 1500 mg/day for ≥ 8 weeks | 7.0%–10.5% (53-91 mmol/mol), inclusive | None. Subjects proceed directly to a combined S2/S3 Visit |
| 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 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 other AHA. Titrate metformin to ≥ 1500 mg/day (if needed). The dose stable period for metformin monotherapy must be ≥ 8 weeks. |

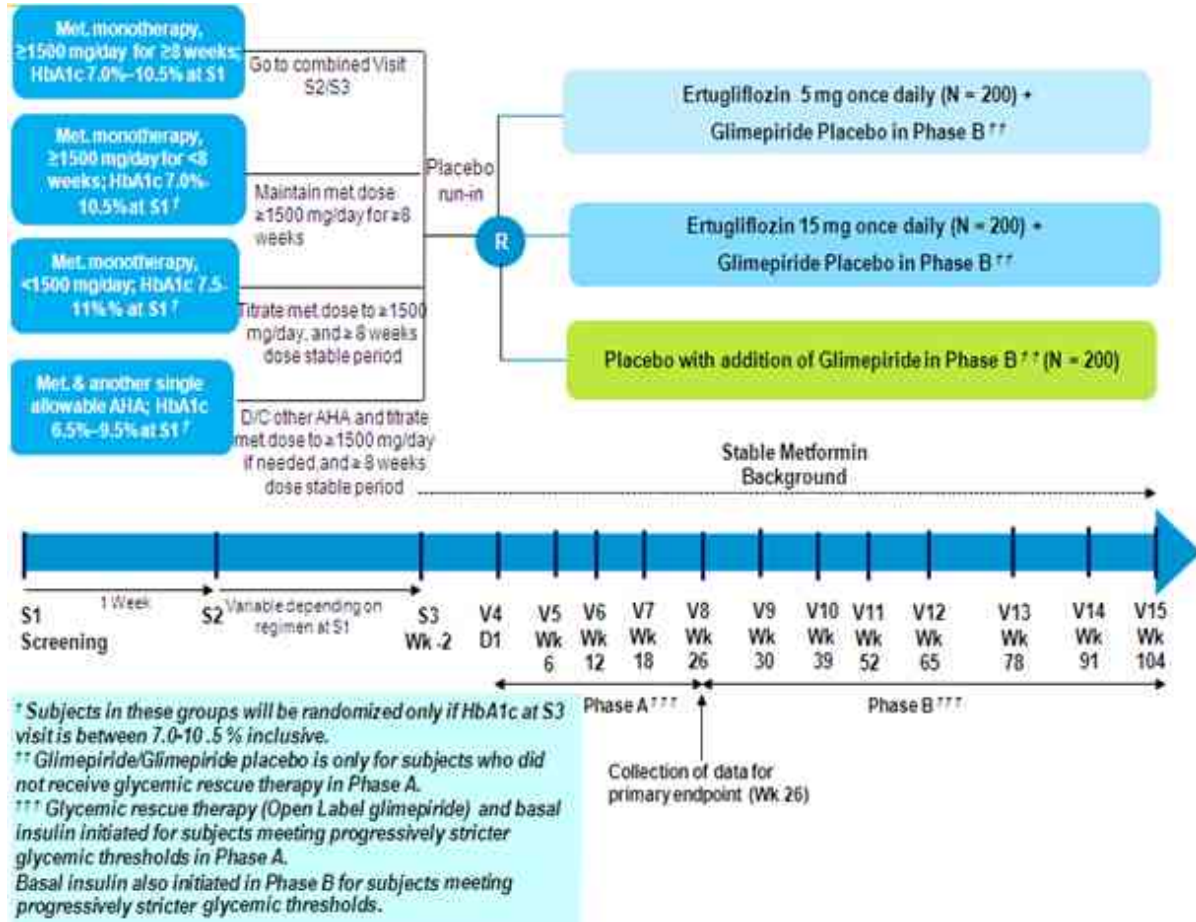
HbA1c = Glycosylated hemoglobin; AHA = Anti-hyperglycemic agent; S1 = Initial screening visit; S2/S3 = Combined Screening Visit 2 and 3.

*allowable AHA agents are sulfonylurea, DPP-4 inhibitor, meglitinide, or alpha-glucosidase inhibitor.

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Figure 1 summarizes the overall trial scheme.

Figure 1. Trial Scheme



Met=Metformin

The trial consists of three phases:

- 1. Screening phase including discontinuation of background diabetes therapy other than metformin (if applicable) and a 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. Phase A: Randomized, double-blind, placebo-controlled treatment period (Visits V4 though V8)** - a 26-week treatment period for assessment of primary and secondary safety and efficacy endpoints. At entry into Phase A, subjects will be randomized to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo, while maintaining metformin at a dose ≥1500 mg/day. Glycemic rescue therapy with open-label glimepiride and basal insulin should be initiated in subjects with glucose values exceeding protocol-specified

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values as mentioned in [Section 5.6](#). Dosing and titration of open-label glimepiride rescue therapy is at the discretion of the Investigator.

3. **Phase B: Double-Blind, extension period (Visits V8 through V15)** – a 78-week, double-blind extension period where subjects randomized to ertugliflozin will remain on their randomized treatment; subjects randomized to placebo will have the addition of treatment with glimepiride (if they were not rescued during Phase A), maintaining the double-blinding; this is accomplished by the use of *blinded glimepiride or matching placebo*, as described below:

- Subjects randomized to ertugliflozin (5 or 15 mg) are continued on their randomized dose of ertugliflozin, *and*
 - If not rescued in Phase A: *will be started* on the addition of placebo matching glimepiride (and with mock uptitration using glimepiride placebo tablets matching 1 or 2 mg tablets, as determined appropriate by the investigator).
 - If rescued in Phase A: *will not be started* on placebo matching glimepiride, and open-label glimepiride will be continued into Phase B.
- Subjects randomized to the placebo treatment group will continue on the placebo tablets matching ertugliflozin *and*
 - If not rescued in Phase A: *will be started* on the addition of glimepiride (1 mg), with titration with 1 or 2 mg tablets (to maximum allowed dose [6 or 8 mg] based upon the local label]) as determined appropriate by the investigator.
 - If rescued in Phase A: *will not be started* on glimepiride, and open label rescue glimepiride will be continued into Phase B.

Note: subjects whose Week 26 visit fasting fingerstick glucose is <110 mg/dL (6.1 mmol/L) will **not** have the glimepiride or matching placebo initiated at the Week 26 visit. At each subsequent scheduled study visit, if the FFSG is \geq 110 mg/dL, glimepiride or matching placebo tablets may be initiated (unless not considered appropriate by the investigator based upon the risk of hypoglycemia).

During Phase B, glycemic rescue therapy with basal insulin should be initiated in subjects with glucose values or HbA1c values exceed protocol-specified values (See [Section 5.6](#)).

A follow-up phone call will take place 14 days after the last dose of investigational product.

This trial is designed to evaluate the efficacy, safety and tolerability of both 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 adult subjects with T2DM and inadequate glycemic control on background treatment with metformin monotherapy.

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It is also designed to evaluate the longer-term efficacy, safety and tolerability of ertugliflozin during the entire 104-week treatment period, which includes a 78-week double-blind extension period. A key purpose of this 78-week double-blind, extension period is to collect additional safety data of ertugliflozin on BMD. The effect of ertugliflozin on BMD will be assessed by DXA. All DXA data throughout the trial will be forwarded to a Central Evaluation Facility to ensure standardization.

Approximately 600 subjects will be randomized to ensure that a minimum of 480 subjects (160 per arm) provide HbA1c data at the Week 26 primary timepoint. Given the plans not to replace those subjects who are withdrawn early, the 600 subjects randomized will control for the approximate 20% premature withdrawal rate for HbA1c data to allow for withdrawn subjects who will still be included in the analysis, but will not necessarily have Week 26 data available. However, a 15% premature withdrawal or non-evaluable rate has been assumed for the BMD data, as this will not be censored if glycemic rescue therapy is taken prior to Week 26. So, the post glycemic rescue therapy data from subjects who require rescue therapy prior to Week 26 will be censored from primary and secondary efficacy analyses. For the bone safety endpoints (BMD and bone biomarkers), all data will be included (including results after glycemic rescue initiation). After the Week 26 visit, Phase A data will be unblinded for limited staff from the Sponsor but not for the Investigator and the subject, or any study team members involved in the day-to-day running of the trial, including site and central monitoring staff.

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. Subjects ≥ 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.¹²
2. Receiving one of the following diabetes therapy regimens at the time of Screening Visit 1 (S1) and with an HbA1c within the following range:

| Diabetes Medication at Screening Visit (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 + sulfonyleurea, 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 AHA therapy at S2) must have an HbA1c of 7.0-10.5% (53-91 mmol/mol) at S3 after at least 8 weeks on a regimen of metformin in monotherapy.
4. Body Mass Index (BMI) 18.0-40.0 kg/m².
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. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
6. 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 4.4.4.1](#) and [4.4.4.2](#) for reference on childbearing potential):
 1. Is postmenopausal defined as at least 12 months with no menses in women ≥ 45 years of age, or
 2. Has had a hysterectomy and/or bilateral oophorectomy, or had bilateral tubal ligation or occlusion at least 6 weeks prior to Screening Visit 1 (S1).
 - c. Is a female of reproductive potential and:
 1. Agrees to remain abstinent from heterosexual activity (if this form of birth control is accepted by local regulatory agencies and ethics review committees as the sole method of birth control for subjects participating in clinical trials), 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

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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). *As an exception, medroxyprogesterone acetate (Depo Provera®) is not permitted.*
- 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).

4.2. 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 or subject assessed by the Investigator as possibly having type 1 diabetes confirmed with a C-peptide <0.7 ng/mL (0.23 nmol/L). **Note:** Only subjects assessed by the Investigator as possibly having type 1 diabetes should have C-peptide measured at Screening Visit 1 (S1).
2. History of secondary 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 Screening Visit 1 (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 Screening Visit 1 (S1), confirmed via 1 repeat triplicate set at Screening Visit 1

(S1) if deemed necessary. 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 be re-assessed for eligibility.

6. Subject has a clinically significant electrocardiogram (ECG) abnormality at Screening Visit (S1) 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 at any time in the past.

13. Subjects with a gender-specific BMD T-score of <-2.5 at any site assessed at Screening Visit 3.
14. Subjects with a documented history of osteoporosis (prior documented BMD T-score of <-2.5).
15. Subjects with rheumatoid arthritis.
16. Subjects with any other illness that could impact BMD assessment such as inherited bone disorders, metabolic bone disease or autoimmune endocrinopathies.
17. Subjects with bilateral hip prosthesis or subjects who have fewer than 3 vertebrae which are evaluable by DXA at Screening Visit 3 (S3).
18. Subjects with hyperparathyroidism defined as a parathyroid hormone (PTH) value at Screening Visit 1 that exceeds the upper limit of the reference range of the central laboratory.
19. Subjects with previously diagnosed atraumatic vertebral fracture or high and low impact fracture of the hip or wrist.
20. Subjects with a known hypersensitivity or intolerance to any SGLT2 inhibitor.
21. Subjects who have previously been randomized in a trial with ertugliflozin.
22. Subjects with a known hypersensitivity or intolerance to glimepiride.
23. 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 (as applicable).
24. Fasting serum triglyceride >600 mg/dL (6.8 mmol/L) at Screening Visit 1 (S1), confirmed by a single repeat if deemed necessary. 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) to lower fasting triglycerides in order for the subject to be re-assessed for eligibility.
25. Subjects taking blood pressure or lipid altering medications that have not been on a stable dose for at least 4 weeks prior to randomization.
26. Subjects currently being treated for hyperthyroidism or subjects on thyroid replacement therapy that has 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 Screening Visit 1 (S1).
27. Male subjects with a serum creatinine ≥ 1.3 mg/dL (≥ 115 $\mu\text{mol/L}$) or female subjects with a serum creatinine ≥ 1.2 mg/dL (≥ 106 $\mu\text{mol/L}$) or subjects with an

eGFR <55 mL/min/1.73m² according to the 4-variable Modification of Diet in Renal Disease (MDRD) equation at Screening Visit 1 (S1).

28. An aspartate transaminase (AST) or alanine transaminase (ALT) >2 X the upper limit of normal (ULN) range at Screening (S1), or a total bilirubin >1.5 X the ULN unless the subject has a history of Gilbert's syndrome.
29. 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.
30. Use of the following prohibited therapeutic agents. These agents are not to be used from 12 weeks prior to Screening Visit 1 (S1) through the completion of the trial:
 - Insulin of any type (except for short-term use during hospitalization or use of basal insulin as glycemic rescue therapy).
 - Other injectable anti-hyperglycemic agents (eg, pramlintide, exenatide, liraglutide).
 - Another SGLT2 inhibitor.
 - Bromocriptine (Cycloset[®]).
 - Colesevelam (Welchol[®]).
 - Any other anti-hyperglycemic therapy with the exception of the protocol-approved agents.
31. The following therapeutic agents are prohibited for the duration of the trial. Specific time length restrictions for each medication/drug class are as follows:
 - Bisphosphonates (eg, alendronate, risedronate, ibandronate, etc): Subjects must not have received a bisphosphonate **for at least 2 years** prior to Screening Visit 1 (S1). The exception to this is subjects who used **an oral** bisphosphonate for <1 month in total so long as the use was not within 12 months of S1.

Note: As an exception, bisphosphonates and other bone active products may be allowed during the study if subjects meet specific rescue criteria related to loss of BMD as described in [Section 7.6.1.1](#).
 - Any other medication or products affecting bone turnover, including but not limited to: calcitonin, parathyroid hormone (teriparatide), estrogen (locally acting estrogen creams are acceptable), testosterone, tamoxifen, raloxifene, bazedoxifene (or another selective estrogen receptor modulators [SERM]), tibolone, denosumab, aromatase inhibitor, strontium, or corticosteroid treatment (oral, inhaled, parenteral at any dose) within 12 months of S1.

- Pioglitazone or rosiglitazone within 12 months of S1 visit.
 - Growth hormone within 12 months of S1 visit.
 - Phenytoin or Phenobarbital within 12 months of S1 visit.
 - Medroxyprogesterone acetate (Depo Provera[®]) within 24 months of S1.
32. 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 completion of the trial.

Note: Topical corticosteroids and physiological replacement doses of adrenal steroids are permitted.

33. 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.
34. Participation in any other trials involving investigational drug(s) (Phase 1-4) within 30 days before Screening Visit 1 (S1) and/or during study participation.
35. 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 Screening Visit (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.
36. 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.
37. 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.
38. 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.
39. Subjects who have donated blood or blood products within six weeks of Screening Visit (S1) or who plan to donate blood or blood products at any time during the trial.

40. Subjects with:

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

41. 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 Criteria

The randomization will be stratified based on post-menopausal status (as well as geographical region -primarily to facilitate drug supply logistics). Approximately 50% of the population enrolled in the trial will be women who have been post-menopausal for 3 years or more (at least 3 years since their last menstrual period [LMP] or bilateral oophorectomy performed 3 years or more prior to screening), and the randomization will be stratified based on this post-menopausal status. The stratification factor will have 4 levels:

- Men.
- Premenopausal women.
- Women who are perimenopausal or post-menopausal for less than 3 years after LMP or bilateral oophorectomy performed less than 3 years prior to screening,
- Women who are post-menopausal for 3 years or more after LMP or women with a history of bilateral oophorectomy performed 3 years or more prior to screening.

Randomization to the men, premenopausal women, perimenopausal or <3 years post-menopausal women groups will be capped at approximately 50% overall, to ensure approximately 50% of randomized subjects are in the group of women who have been post-menopausal for 3 years or more after LMP, or with a history of bilateral oophorectomy performed 3 years or more prior to screening.

Subjects will be assigned a unique identifier via an Interactive Voice Response System (IVRS) at Screening Visit (S1), which will be retained throughout the duration of their participation in the trial. Subjects who have discontinued a diabetes medication at S2 or needed a change in their metformin dose at S2 or who were not on metformin ≥ 1500 mg/day for ≥ 8 weeks at S2 are required to have an HbA1c measurement at S3 to determine eligibility as defined in the inclusion criteria. These subjects will start the placebo run-in at S3 but can only be randomized on Day 1 (V4) if the S3 HbA1c meets the entry requirement. Subjects will be randomized into the study at V4, provided that they have satisfied all subject eligibility criteria. Eligibility criteria are outlined in [Sections 4.1](#) and [4.2](#) and should be verified at S1, S2 and S3 as applicable. A computer-generated randomization code using the

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method of random permuted blocks will be utilized to assign on Day 1 (V4) subjects to 1 of the 3 treatment regimens (ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo). The same randomization code will then be used to assign blinded glimepiride/placebo therapy for Phase B.

4.4. Life Style Guidelines

4.4.1. Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least **10 hours** prior to any blood sample collections for clinical laboratory tests, fasting glucose monitoring, 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, rescue therapy (if applicable), or blinded glimepiride/placebo. 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 (SOA).
- 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.

4.4.2. 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.

4.4.3. Alcohol, Caffeine and Tobacco

- Intake of alcohol should be limited (refer to exclusion 9 for acceptable amount of alcohol consumption).
- Ingestion of caffeine will be prohibited for at least 30 minutes prior to scheduled electrocardiograms and blood pressure determinations.
- Ingestion of nicotine-containing products will be prohibited for at least 30 minutes prior to the scheduled electrocardiogram and blood pressure determinations.

4.4.4. 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 4.4.4.2 will be allowed to enroll in this trial.

4.4.4.1. Females– Non-childbearing Potential

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

- 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 Screening Visit (S1).

4.4.4.2. Females of Childbearing Potential

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

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. As an exception, medroxyprogesterone acetate (Depo Provera[®]) is not permitted.
- Use of an IUD with one of the following: condom; diaphragm with spermicide; contraceptive sponge; vasectomy; or hormonal contraception (see above).
- Vasectomy with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; IUD; or hormonal contraception (see above).

4.5. Sponsor Qualified Medical Personnel

The contact information for the Sponsor's appropriately qualified medical personnel for the trial is documented in the 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 600 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. 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.

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Phase A of this trial is subject-, Investigator-, and sponsor-blinded. Following completion of Phase A (defined as database lock), treatment assignment for subjects in Phase A of the trial will become available to limited staff from Pfizer/Merck and their delegates to permit authoring of the clinical study report. Phase B of the trial will be blinded to the subject, Investigator, and Sponsor or Sponsor-designate personnel responsible for study monitoring activities (including all site monitoring activities).

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 in Phases A and B. Tablets will be packaged into bottles or blister cards.

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 run-in will be administered starting at Day -14/Visit S3 where subjects will be instructed to take 1 tablet of placebo ertugliflozin 5 mg and 1 tablet of placebo ertugliflozin 10 mg each day from the bottles or blister card(s) 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) and Extended Release (ER) forms are allowed in the study, provided that the same subject remains on the same formulation (IR or ER) from S2 to the Week 104 visit.

Metformin titration will be required for some subjects between Screening Visit 2 (S2) and Screening Visit 3 (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.

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Those subjects will enter the placebo run-in period at S3 after the metformin monotherapy dose of ≥ 1500 mg/day has been kept stable for at least 8 weeks.

The metformin dose will not be changed from Screening Visit 3 until the end of the trial (V15), except if medically necessary. In that case, all efforts should be made to get the subject back to the previous dose.

5.3.4. Administration (Ertugliflozin/Placebo)

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 or blister cards and given clear dosing instructions. They will be instructed to take 2 tablets per day of ertugliflozin/placebo, one from each bottle or blister card. 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 104 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.

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. Drug Supplies for Phase B

The Sponsor will supply blinded glimepiride and matching placebo for glimepiride, for oral administration, as 1 mg and 2 mg strength over-encapsulated tablets or matching placebo.

Blinded glimepiride and matching placebo for glimepiride will only be provided to subjects who **were not** rescued in Phase A with open-label glimepiride. At entry into Phase B, **non-rescued** subjects in the placebo treatment group will receive blinded glimepiride in addition to placebo for ertugliflozin while **non-rescued** subjects in the ertugliflozin groups will receive a matching placebo for glimepiride.

Glimepiride/placebo will be supplied in bottles for dispensing at each visit containing sufficient supplies to permit dosing until the next scheduled visit. Glimepiride/placebo should be stored in accordance with the label. All blinded glimepiride and matching placebo for glimepiride 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.

5.3.5.1. Administration of Glimepiride/Matching Placebo

The dose of glimepiride/matching placebo will be initiated at 1 mg/day (or matching placebo for 1 mg tablet) starting on the day of the Week 26 visit for subjects who were not rescued in Phase A, and only if subject's fasting fingerstick glucose (FFSG) at Week 26 visit is ≥ 110 mg/dL (6.1 mmol/L).

If the subject's FFSG at Week 26 visit is < 110 mg/dL (6.1 mmol/L), the subject will not receive glimepiride/matching placebo at the Week 26 visit.

All subjects will continue with investigational product (ertugliflozin/placebo) during Phase B, regardless of whether a subject does or does not initiate glimepiride/matching placebo at Week 26.

For subjects started on glimepiride/matching placebo 1 mg at Week 26, at the Week 30 visit, the dose of glimepiride/matching placebo will be increased to 2 mg once daily (QD), if deemed appropriate by the Investigator based on the subject's self-monitoring blood glucose measurements and assessment of risk of hypoglycemia. Assessment of glimepiride dosing will then take place at subsequent clinic visits (ie, Weeks 39, 52, 65, 78, and 91). Further up-titration of glimepiride will be made in increments of 2 mg/day, with the maximum dose (6 or 8 mg QD) based upon the local label of glimepiride. Subjects may remain on 1 mg/day if appropriate based on finger-stick glucose monitoring.

Subjects who did not have glimepiride/matching placebo initiated at the Week 26 visit may have glimepiride/matching placebo initiated (with 1 mg dose) at any subsequent visit, if their FFSG is no longer < 110 mg/dL (6.1 mmol/L), and subsequently uptitrated, as described above. Down-titration is allowed at any time during the trial, as needed, in order to avoid hypoglycemia.

It is recommended that the dose of glimepiride be administered with breakfast or the first main meal of the day.

If any adjustment in the administration of glimepiride/matching placebo is necessary between scheduled visits, an unscheduled visit to the site should be performed.

In case of hypoglycemia:

If a subject experiences episodes of unexplained hypoglycemia (ie, not explained by missed meals or excess physical activity), the subject's glimepiride/matching placebo should be down-titrated to a dose determined appropriate by the Investigator. In general, glimepiride should be down-titrated by 2 mg/day (eg, 6 mg to 4 mg or 4 mg to 2 mg), or more rapidly, as considered appropriate by the Investigator. In subjects receiving 2 mg/day the dose should be reduced to 1 mg/day in case of hypoglycemia. Subjects on glimepiride/matching placebo 1 mg who experience unexplained hypoglycemia should interrupt glimepiride/matching placebo and may continue in the trial off of glimepiride/matching placebo. If unexplained hypoglycemia continues to occur after glimepiride/matching placebo is interrupted, the subject should be considered for discontinuation from the blinded investigational product

according to [Section 6.7.2](#) – Reason for Discontinuation from Investigational Product or From the Study.

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

Note: If glimepiride/matching placebo is re-initiated, the dose should not be up-titrated beyond the dose at which hypoglycemia originally occurred.

5.3.6. Compliance

Subjects will be directed to bring any used and unused bottles or blister cards 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 = $100 \times (\text{tablets dispensed} - \text{tablets returned}) / \text{No. of days between visits} \times \text{No. of tablets taken per day}$

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, and blinded glimepiride/placebo therapy (if applicable) 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.

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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](#).

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 exclusion criterion 25. 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 warranted.

Subjects who are receiving calcium supplementation upon entry into the trial should continue to receive these medications at the same doses throughout the trial. The concentration of 25-hydroxyvitamin D will be measured at S3. Based on the results, the Investigator will be allowed to supplement subjects with vitamin D according to local practices or country dietary guidelines and if clinically necessary.

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.

5.6. Glycemic Rescue Therapy

Subjects will be prescribed open-label glycemic rescue therapy and dosed according to physician judgment, if they meet specific, progressively more stringent, glycemic thresholds based on a **repeated, confirmed** FPG or HbA1c measured by the **central lab** according to the directions below:

Table 4. Glycemic Thresholds

| | |
|--------------------------------|---|
| Randomization through Week 6: | FPG >270 mg/dL (15.0 mmol/L) |
| After Week 6 through Week 12: | FPG >240 mg/dL (13.3 mmol/L) |
| After Week 12 through Week 26: | FPG >200 mg/dL (11.1 mmol/L) |
| After Week 26: | FPG >200 mg/dL (11.1 mmol/L) or HbA1c >8.0% (64 mmol/mol) |

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).

During Phase A, subjects exceeding pre-specified glycemic thresholds after randomization will have glycemic rescue therapy initiated with open-label glimepiride. Glycemic rescue therapy 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. Dosing will be at the Investigator's discretion and the Investigator will be responsible for managing the initiation and titration of the glimepiride rescue therapy according to 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 6.6](#).

Subjects requiring glycemic rescue therapy during Phase A and entering into Phase B are to remain in the trial up to the end, and will continue to receive investigational product (ertugliflozin/placebo) in a blinded fashion as well as open-label glimepiride. These subjects will not receive blinded glimepiride/placebo therapy during Phase B.

Additional glycemic rescue therapy with basal insulin should be initiated as follows:

During Phase A (prior to Week 26 visit):

- *Subjects who were initiated on open-label glimepiride rescue therapy, and who reached the maximum allowed dose (or tolerated dose, if lower), who meet glycemic rescue FPG criteria (after at least 2 weeks on maximum dose of glimepiride), will have basal insulin initiated and managed as considered appropriate by the investigator (ie, including selection of agent and starting dose, timing of administration, and uptitration).*

During Phase B:

- *Subjects who were initiated on open-label glimepiride rescue therapy in Phase A, who meet glycemic rescue criteria after at least 2 weeks on maximum dose of*

open-label glimepiride for FPG criteria or at least 8 weeks for HbA1c criteria, will have basal insulin initiated and managed as considered appropriate by the investigator (ie, including selection of agent and starting dose, timing of administration, and up-titration).

- *Subjects not on Phase A open-label glimepiride rescue therapy* who meet glycemic rescue criteria after at least 2 weeks on maximum dose of blinded glimepiride or matching placebo for FPG criteria or at least 8 weeks for HbA1c criteria will have basal insulin initiated and managed as considered appropriate by the investigator (ie, including selection of agent and starting dose, timing of administration, and up-titration).

Basal insulin 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. Consideration should be given to reducing the dose of glimepiride (either open-label, for rescued subjects, or blinded glimepiride or matching placebo, for non-rescued subjects) as basal insulin treatment is initiated and up-titrated.

5.6.1. Drug Supplies for Glycemic Rescue Therapy

During Phase A, subjects requiring glycemic rescue therapy will receive treatment with open-label glimepiride. Open-label glimepiride will be provided locally by the trial site or subsidiary, depending on local country operational or regulatory requirements.

For subjects requiring rescue therapy with basal insulin (eg, insulin glargine, insulin detemir, NPH insulin, degludec), basal insulin will be provided 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 obtained before or after blood specimen collection.
- Visit windows for this trial are recommended and not required.

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

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

At S2, 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 visit only; monitoring at other visits may be done by other appropriate site personnel evaluating the subject.

At S2, the subject will receive counseling on diet consistent with the local guidelines of the country of the investigational site. At each subsequent visit, the subject will be asked about their diet and exercise. Detailed dietary information will not be captured.

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

6.2. Screening

6.2.1. Screening Visit 1 (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). The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
- Contact IVRS.
- 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; chemistry, hematology, urinalysis [refer to [Section 7.4.1](#)].
- HbA1c, fasting plasma glucose (FPG), fasting triglycerides, TSH, PTH.
- Urine pregnancy test for women of childbearing potential.
- Fasting C-peptide (only for subjects assessed by the Investigator as possibly having type 1 diabetes).
- Perform an optional fingerstick HbA1c assessment while at the site. The fingerstick HbA1c cannot substitute for a central laboratory measurement to determine subject eligibility.
- Review of eligibility criteria.

Subjects must be instructed to continue their background oral AHA; no changes to background oral AHA (if applicable) will be made until the S2 Visit.

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 (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 ≥ 1500 mg/day for 8 weeks or more at S1 can proceed with a **combined S2/S3 Visit**. For combined visits, all procedures from each individual visit must be performed at the one combined visit.

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 supine, single, standard, 12-lead ECG [refer to [Section 7.4.4](#)].
- 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 these symptoms occur and/or worsen before next visit (ie, S3).

- Subjects will be provided with a hypoglycemia assessment log that they must use to track the incidence of hypoglycemia. Subjects should be educated on the symptoms of hypoglycemia [refer to [Section 6.1.1](#)] and instructed to call the site should these symptoms occur and/or worsen before next visit (ie, S3).
- 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.

Subjects receiving metformin in combination with one other allowable AHA must discontinue this other AHA beginning at the S2 visit and remain off this other AHA for the duration of this trial.

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 ≥ 1500 mg/day for 8 weeks or more at S1 can proceed with a **combined S2/S3 Visit**. If visit is combined 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.
- Measure HbA1c to assess eligibility for subjects taking metformin monotherapy for less than 8 weeks at the S1 visit and for those who required a change to their diabetes regimen at the S2 visit (including subjects who have discontinued their AHA therapy at the S2 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?”
- DXA of lumbar spine, total hip, femoral neck and distal forearm [refer to [Section 7.6](#)]. DXA should be performed on the same day as the S3 visit. However, if it cannot be performed on this day, the DXA will need to be conducted sometime between S3 and at least ten days before the Day 1 visit in order that the results will be available prior to Day 1.
- Perform complete physical examination [refer to [Section 7.3](#)].

- 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](#)].
- Obtain blood sample for 25-hydroxyvitamin D measurement.
- Urine pregnancy test for women of childbearing potential.
- Perform a fasting finger stick blood glucose assessment at the clinic.
- 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. Phase A: Double-Blind, Placebo-Controlled Treatment Period (Visits 4 through 8)

6.3.1. Day 1 (Visit 4)

At 14 days \pm 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 or blister card(s) 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 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](#)].
 - 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](#)].
 - 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](#)] including chemistry, hematology, urinalysis, urinary albumin/creatinine ratio, urine pregnancy test (where applicable) [refer to [Section 7.1](#)], lipid panel, apolipoproteins, HbA1c, FPG, and whole blood (DNA), plasma and serum for Future Biomedical Research (FBR) [refer to [Schedule of Activities Table](#) and [Appendix 1](#)].
- Note: The FBR sample for DNA analysis should be obtained pre-dose, at Day 1/Visit 4, as the last sample drawn, on subjects who qualify for randomization, but may be obtained at a later date during the trial after the FBR informed consent is obtained. The plasma and serum samples for FBR should be collected at Day 1 (pre-dose).
- Bone Biomarkers (CTX, P1NP) and PTH [refer to [Section 7.7](#)].

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 6 weeks \pm 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 7.8](#)].
- 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](#)] including chemistry, urine pregnancy test (where applicable) [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 glycemic rescue therapy, if applicable.
- Dispense investigational product.

6.3.3. Week 12 (Visit 6)

At 12 weeks ± 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 7.8](#)].
- 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](#)] including chemistry, hematology, urine pregnancy test (where applicable) [refer to [Section 7.1](#)], lipid panel, 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 samples are 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.
- 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.

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

6.3.4. Week 18 (Visit 7)

At 18 weeks \pm 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 7.8](#)].
- 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](#)] including chemistry, urine pregnancy test (where applicable) [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.
- 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).

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- Contact IVRS.
- Dispense glycemic rescue therapy, if applicable.
- Dispense investigational product.

6.3.5. Week 26 (Visit 8)

At Week 26 \pm 7 days relative to Day 1 (V4), subjects will return to the site after a minimum **10-hour fast** (except water) for V8. Completion of the Week 26 (V8) visit marks the end of the subjects' participation in Phase A and entry into Phase B (double-blind extension). At this visit, the following procedures will be completed **prior** to administration of investigational product:

- Assess treatment compliance with investigational product and counsel subject for non-compliance, as needed.
- Review and update concomitant medications since last visit.
- 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 brief physical examination which includes assessment of heart, lungs, abdomen, extremities and skin.
- Obtain triplicate orthostatic blood pressure and pulse rate measurement (supine \rightarrow standing [refer to [7.4.3](#)].
- Obtain supine, single, standard, 12-lead ECG [refer to [Section 7.4.4](#)].
- Perform DXA of lumbar spine, total hip, femoral neck and distal forearm [refer to [Section 7.6](#)]. If the DXA can't be performed at Week 26 visit, it can be obtained \pm 7 days from the scheduled visit date.
- 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 7.8](#)].
- 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 at the clinic.
- Diet and exercise monitoring (see [Section 6.1.2](#)).

- Obtain blood **and** urine specimens for:
 - Clinical laboratory tests [refer to [Section 7.4.1](#)] including chemistry, hematology, urinalysis, urinary albumin/creatinine ratio, urine pregnancy test (where applicable) [refer to [Section 7.1](#)], lipid panel, apolipoproteins, HbA1c, FPG and FBR plasma and serum samples [Appendix 1](#).
 - Bone Biomarkers (CTX and P1NP) and PTH [refer to [Section 7.7](#)].

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.
- Subjects will be dispensed drug supplies to last them to the next visit:
 - Double-blind investigational product for ertugliflozin/placebo; AND
 - Blinded glimepiride/placebo therapy only to subjects NOT receiving open-label glimepiride for glycemic rescue and whose fasting fingerstick glucose (FFSG) at Week 26 visit is ≥ 110 mg/dL (6.1 mmol/L).
- Week 26 dose of double-blind ertugliflozin/placebo will be administered from new supply of investigational product and witnessed in clinic.
- Dispense glycemic rescue therapy, if applicable.

6.4. Phase B: Double-Blind Extension Period (Visits 8 through 15)

This blinded (sponsor-open), double-blind extension period starts after the completion of the Week 26 assessments for Phase A (V8) and includes Visits 9 through 15 conducted at Weeks 30, 39, 52, 65, 78, 91, and 104.

6.4.1. Week 30 (Visit 9)

At 30 weeks ± 7 days relative to Day 1 (V4), subjects will return to the site after a minimum **10-hour fast** (except water) for V9. At this visit, the following procedures will be completed:

- Contact IVRS.
- Update concomitant medications since last visit.
- 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 7.8](#)].

- Perform a fasting finger stick blood glucose assessment at the clinic.
- Obtain plasma sample for pharmacokinetics of ertugliflozin [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.
- Review self-monitoring blood glucose and Hypoglycemia Assessment Logs completed by the subject [refer to [Section 7.4.6](#)].
- Subjects will be dispensed the following drug supply to last them to the next visit:
 - Blinded glimepiride/placebo therapy (applicable only to subjects who are NOT receiving open-label glimeperide for glycemic rescue).

6.4.2. Week 39 (Visit 10) through Week 91 (Visit 14)

Visits following Week 30 have a visit window of ± 14 days relative to Day 1. The procedures for Visits 10-14 are described in this section.

Additional procedures are required for Week 52 (V11), which are further defined in [Section 6.4.3](#), respectively.

Following the preceding visit and within the corresponding visit window, subjects will return to the site after a minimum **10-hour fast** (except water) for V9-14. At these visits, the following procedures will be completed:

- Update concomitant medications since last visit.
- Assess treatment compliance with investigational product and blinded glimepiride/placebo therapy (if applicable), 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 7.8](#)].
- 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](#)).

- Perform a fasting finger stick blood glucose assessment at the clinic.
- Obtain blood **and** urine specimens for:
 - Clinical laboratory tests [refer to [Section 7.4.1](#)] including chemistry; hematology (only at Week 52 and Week 78); urinalysis (only at Week 52 and Week 78); urine pregnancy test (where applicable) [refer to [Section 7.1](#)]; HbA1c; and FPG.

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.
- Subjects will be dispensed drug supplies to last them to the next visit:
 - Double-blind investigational product for ertugliflozin/placebo; AND
 - Blinded glimepiride/placebo therapy (applicable only to subjects who are NOT receiving open-label glimeperide for glycemic rescue).
- Dispense glycemic rescue therapy, if applicable.

6.4.3. Week 52 (Visit 11)

At Week 52 \pm 14 days relative to Day 1 (V4), after a minimum 10-hour fast (except water), the following procedures will be completed **in addition** to those previously listed in [Section 6.4.2](#):

- Conduct brief physical examination which includes assessment of heart, lungs, abdomen, extremities and skin.
- Obtain supine, single, standard, 12-lead ECG [refer to [Section 7.4.4](#)].
- Perform DXA of lumbar spine, femoral neck, total hip, and distal forearm [refer to [Section 7.6](#)]. If the DXA can't be performed at Week 52 visit, it can be obtained \pm 7 days from the scheduled visit date.
- Obtain blood **and** urine specimens for:
 - Urinalysis, urinary albumin/creatinine ratio, lipid panel.
 - Bone Biomarkers and PTH [refer to [Section 7.7](#)].

6.4.4. Week 104 (Visit 15) – Final Study Visit/Early Termination Visit

At Week 104 \pm 14 days relative to Day 1 (V4) or at Early Termination (ET), subjects will return to the site after a minimum **10-hour fast** (except water).

Completion of the Week 104 (V15) visit marks the end of the subject's participation in Phase B. Subjects who complete the trial and those who discontinue from the trial prematurely, should complete the procedures listed below:

- Contact IVRS.
- Update concomitant medications since last visit.
- Assess treatment compliance with investigational product and blinded glimepiride/placebo therapy (if applicable).
- 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](#)].
- Obtain supine, single, standard, 12-lead ECG [refer to [Section 7.4.4](#)].
- DXA of lumbar spine, total hip, femoral neck and distal forearm [refer to [Section 7.6](#)]. If the DXA can't be performed at Week 104 visit, it can be obtained in a 7 days window prior to Week 104. In case of discontinuation of investigational product during Phase A, a DXA scan will be performed if the discontinuation occurs between Week 12 and Week 26. In case of discontinuation of investigational product during Phase B, a DXA scan will be performed if the discontinuation occurs at least 12 weeks from the previous scan.
- Conduct brief physical examination which includes assessment of heart, lungs, abdomen, extremities and skin.
- 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 7.8](#)].
- 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 at the clinic.
- Diet and exercise monitoring (see [Section 6.1.2](#)).
- Obtain blood **and** urine specimens for:

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- Clinical laboratory tests [refer to [Section 7.4.1](#)] including chemistry, hematology, urinalysis, urinary albumin/creatinine ratio, urine pregnancy test (where applicable) [refer to [Section 7.1](#)], lipid panel, HbA1c (only if visit is at least 6 weeks after randomization), apolipoproteins (at early termination visit only), FPG, FBR plasma and serum samples ([Appendix 1](#)).
- Bone Biomarkers (CTX, P1NP) and PTH [refer to [Section 7.7](#)].

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 104 visit unless they withdraw consent per [Section 6.7](#).

6.5. 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 7.8](#), if applicable. The phone call should be completed within a ± 3 day window.

6.6. 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. If subjects require glycemic rescue therapy prior to Week 6, a rescue visit should occur. The following procedures are to be completed at a rescue 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 measurement of sitting blood pressure and pulse rate [refer to [Section 7.4.2](#)].
- Obtain duplicate orthostatic blood pressure and pulse rate measurement (supine \rightarrow standing) [refer to [Section 7.4.3](#)] only if the Rescue Visit occurs in Phase A.
- Conduct brief physical examination which includes assessment of heart, lungs, abdomen, extremities and skin.
- 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), apolipoproteins, FPG and FBR plasma and serum samples.
- 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.
- Diet and exercise monitoring (see [Section 6.1.2](#)).
- Dispense glycemic rescue therapy as appropriate. Dosing of open-label glimepiride and basal insulin is at the Investigator's discretion.
- Distribute glucose meter and supplies, as needed.

6.7. 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.

If a subject indicates his or her intention to stop active participation (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) in the trial 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 7.8](#)]). 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 study drug 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

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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.

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 or insulin (for those rescued) until trial completion. The Investigator should ensure that the subject has enough open-label rescue medication until the next scheduled in clinic visit. Procurement of any other oral AHAs, is the responsibility of the subject.

6.7.1. Withdrawal from Future Biomedical Research

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

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

6.7.2. 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).

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- Death.

Discontinuation of Investigational Product

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

Subject continues to exceed glycemic rescue criteria for at least 3 weeks despite maximal adjustment of basal insulin therapy, without a reasonable explanation (eg, intercurrent illness or medication omission). Subjects who don't agree to start basal insulin will have investigational product discontinued.

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).

Note: For subjects rescued with glimepiride and/or basal insulin, the protocol-specified discontinuation criteria for hypoglycemia only apply after the subject has interrupted glycemic rescue medication. Similarly, for subjects who were started on Phase B blinded glimepiride or matching placebo, the hypoglycemia criteria only applies when subject is off of blinded glimepiride or matching placebo.

3. Abnormal liver function tests meeting 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 m² (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. See [Section 6.7.2.1](#) 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 4.2](#).
6. For subjects who are on glycemic rescue medication, if such a subject develops any condition for which the rescue medication 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 7.1](#) 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).

If a subject discontinues investigational product, he/she should complete all Early Termination Visit procedures as described in [Section 6.4.4](#) 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 104. Such subjects may initiate other AHA therapy as indicated (prohibited medications described in [Section 5.5](#) will not apply to these subjects.)

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

Subjects who discontinue blinded investigational product for eGFR/creatinine discontinuation criteria (see [Section 6.7.2](#)) or renal-related adverse events should have a repeat eGFR/creatinine performed 1 week after the last dose of Investigational Product. This post-treatment visit may occur at the Discontinuation visit (if the Discontinuation visit occurs 1 week after the last dose of Investigational Product) or at an unscheduled visit. The out of range test(s) should continue to be repeated at intervals, as considered appropriate (eg, weekly or every other week) until the value returns to baseline (pre-randomization value) or a new baseline is established. The Investigator should implement an appropriate evaluation for events of clinically significant change in eGFR (eg, >30% reductions in eGFR from baseline values). Such an evaluation should include detailed review of any associated symptoms, thorough review of concomitant medications (including “over the counter” agents) to determine if the subject had any change (new initiation or change in dose) in his or her medication regimen with agents associated with decreases in eGFR (eg, non-steroidal anti-inflammatory agents, fenofibrate, 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 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 104 visit. Pregnancy tests may also be repeated as per request of IRB/IECs 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 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, extremities, and skin 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 | BUN | pH | <i>At SI only:</i> |
| Hematocrit | Serum Creatinine | Protein (qual) | - Fasting triglycerides/TSH |
| RBC Count | Ca ⁺⁺ (total) | Blood (qual) | |
| Platelet Count | Na ⁺ | Ketones | <i>At selected visits, only (refer to</i> |
| WBC Count | K ⁺ | Leukocyte esterase | <i>Schedule of Activities):</i> |
| Total Neutrophils (Abs) | Cl ⁻ | Nitrites | - PTH, CTX, PINP |
| Eosinophils (Abs) | Total CO ₂ (Bicarbonate) | Microscopy ^d | - 25-hydroxyvitamin D |
| Monocytes (Abs) | Mg ⁺⁺ | | -HbA1c |
| Basophils (Abs) | Phosphate | | - FPG |
| Lymphocytes (Abs) | Uric Acid | | - C-peptide |
| | AST (SGOT) | | - Urinary albumin/creatinine ratio ^e |
| | ALT (SGPT) | | - Pregnancy tests (where |
| | Alkaline Phosphatase | | applicable) |
| | Total bilirubin | | - Lipid panel (ie, total cholesterol, |
| | Direct (conjugated) bilirubin ^b | | HDL, LDL, triglycerides) |
| | Indirect (unconjugated) bilirubin ^c | | - Apolipoproteins (ApoB, and |
| | Albumin | | ApoA-1) |
| | Total Protein | | |

- Routinely collected samples for urinalysis will be sent to the central laboratory for dipstick analysis and microscopy if needed, see [d].
- Direct bilirubin measured only when total bilirubin is greater than upper limit of normal.
- Indirect bilirubin measured only when total bilirubin is greater than upper limit of normal.
- Microscopy to be performed by central laboratory if dipstick is positive for blood, nitrites, leukocytes and/or protein. Subjects found to have microscopic hematuria (defined as the presence of three or more red blood cells per high powered field on microscopic examination) from a properly collected, non-contaminated urinalysis with no evidence of infection, should be referred to a urologist for appropriate work-up.
- 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 and Apolipoproteins

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.
- ApoB and ApoA-1 will also be included at Day 1 and Week 26 visits as well as the glycemic rescue visit and early termination visit.

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 and Week 26 visits, duplicate measurements of supine and standing blood pressure and pulse rate will be taken in order to evaluate postural changes in blood pressure and pulse rate. These measurements will be in addition to the sitting blood pressure and pulse rate measurements taken on these clinic visits (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 screening ECG should be read and interpreted at the investigative site. ECGs performed at Day 1 and time points after randomization should be reviewed at the investigative site for subject safety monitoring, as well as electronically transmitted to a central vendor for reading and interpretation centrally. The Investigator is responsible for retaining all copies of the ECG reports.

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 call the site should these symptoms occur and/or worsen before next visit.

A subject should be discontinued from the investigational product 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).

Any episode of hypoglycemia must be captured on the Hypoglycemic Adverse Event 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.

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 finger-stick or plasma 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. 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 30. 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.

As part of understanding the pharmacokinetics of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal (ie, Sponsor) exploratory purposes and will not be included in the clinical study report.

7.6. Dual-Energy X-Ray Absorptiometry (DXA)

7.6.1. Bone Mineral Densitometry

Bone densitometry will be performed in facilities qualified and approved by the Sponsor or its designee.

DXA scanning procedures will be standardized and all the scans will be monitored and centrally analyzed by a Central Evaluation Facility according to a specific protocol. Procedures to be followed by the bone densitometry facilities to maintain quality control will be provided in a separate manual. The hardware used should remain the same for the duration of the trial. Software upgrades to DXA equipment must be approved in advance by the Central Evaluation Facility.

BMD of lumbar spine (L₁-L₄), femoral neck, and total hip and distal forearm will be measured by DXA at all time-points as mentioned in the [Schedule of Activities](#). The left hip should be evaluated unless prevented by pathology, in which case the right hip will be evaluated throughout the trial.

Screening DXA scan should be performed at Screening Visit 3, or sometime between S3 and at least ten days before the Day 1 visit. These scans will be submitted to the Central

Evaluation Facility for assessment of eligibility. Assessment of eligibility will be returned to the site before Day 1 visit and results of the Screening DXA must be available prior to subject randomization.

Follow up DXA scans will be performed at Week 26, 52 and 104 visits and submitted to the Central Evaluation Facility for assessment. Follow-up scans should be obtained in a ± 14 day window from the scheduled Week 26, 52 visits and in a 14 day window prior to the Week 104 visit. Investigators will remain blinded to the results of these follow up scans, unless the subject meets criteria for rescue criteria as provided below.

In case of discontinuation of investigational product during Phase A, a DXA scan will be performed if the discontinuation occurs between Week 12 and Week 26. In case of discontinuation of investigational product during Phase B, a DXA scan will be performed if the discontinuation occurs at least 12 weeks from the previous scan.

7.6.1.1. Rescue Criteria Related to Loss of BMD

Rescue criteria will be put into place for subjects who exhibit a significant reduction in BMD according to the protocol-defined criteria. Subjects with a reduction in BMD from baseline of $>7\%$ at any anatomical site together with a T-score <-2.5 at the Week 26 or Week 52 follow-up scans, will have a complete unscheduled DXA performed. If these values are confirmed based on a repeat, complete unscheduled DXA the Investigator or treating physician will be permitted to start any bone active therapy. In these cases, subjects should continue to receive ertugliflozin or matching placebo. The repeat, confirmatory DXA should be performed within 4 weeks from the initial reading.

7.7. Bone Biomarkers, PTH

Blood will be collected for analysis of biochemical markers of bone turnover. The following biomarkers will be measured during the study at the times listed in the [Schedule of Activities](#).

- Carboxy-terminal cross-linking telopeptides of Type I collagen (CTX); measured as a biomarker of bone resorption.
- Procollagen type I N-terminal propeptide (P1NP); measured as a marker of bone formation.

Parathyroid hormone (PTH) will also be measured according to the times in the [Schedule of Activities](#).

The sample(s) for measurement of bone biomarkers and PTH should not be collected if the investigational product has been discontinued for >7 days prior to the collection of the sample(s).

7.8. Clinical Event Adjudication

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

The identification of a potential clinical cardiovascular event, venous thrombo embolic 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 regulatory requirements for the assessment of cardiovascular safety of any new diabetic therapy, serious cardiovascular events and all deaths will be adjudicated in this trial (including events from subjects who continue to be followed after discontinuation of investigational product), and across the Phase 2 and 3 ertugliflozin program. The Endpoint Adjudication Committee (EAC) will be comprised of an external panel of independent physicians experienced in assessing cardiovascular endpoints. The panel will be blinded to treatment assignments. The members of the EAC will not be an Investigator in any trial for ertugliflozin. The events to be adjudicated by the committee include:

1. All deaths.
2. Non-fatal myocardial infarction; hospitalization for chest pain or to rule out myocardial infarction, or other hospitalization due to suspected myocardial ischemia where myocardial infarction needs to be ruled out.
3. Non-fatal stroke (and all events that may be a stroke including all transient ischemic attack (TIA) events, reversible ischemic neurologic deficit (RIND) or other acute ischemic cerebrovascular event where stroke needs to be ruled out).
4. Hospitalization for unstable angina.
5. Hospitalization for heart failure.
6. Venous thromboembolism/pulmonary embolus.

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

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

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Pfizer or designee will 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.

7.8.2. Fractures

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

7.8.3. 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.

7.8.4. 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.

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7.8.5. Acute Renal Failure

Ertugliflozin, an SGLT2 inhibitor, increases urinary glucose excretion leading to an osmotic diuresis, and has the potential to reduce estimated glomerular filtration rate (eGFR). 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 unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (ie, any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

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

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

Adverse events may occur 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.

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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 another 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 | Mild | awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated) |
| Intensity | 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 †). | | |

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| | | |
|-----------------------------------|--|--|
| 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 | <p>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.</p> <p>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:</p> | |
| | 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 | <p>Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product?</p> <p>Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?</p> |
| | 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 | The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued) | |
| (continued) | Dechallenge | <p>Was the Sponsor's product discontinued or dose/exposure/frequency reduced?</p> <p>If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge.</p> <p>(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.)</p> |

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| | |
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| Rechallenge | <p>Was the subject re-exposed to the Sponsor's product in this trial?</p> <p>If yes, did the AE recur or worsen?</p> <p>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.</p> <p>(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.)</p> <p>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.</p> |
| Consistency with Trial Treatment Profile | <p>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?</p> |
| <p>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.</p> | |
| Record one of the following: | <p>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).</p> |
| Yes, there is a reasonable possibility of Sponsor's product relationship. | <p>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.</p> |
| No, there is not a reasonable possibility of Sponsor's product relationship | <p>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.)</p> |

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 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 $\geq 3X$ ULN)

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

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

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

Investigator Instructions for Management of Subjects with ALT or AST $\geq 3X$ ULN

| |
|---|
| A) Subject has: <ul style="list-style-type: none">• ALT or AST $\geq 3X$ ULN with TBL $\geq 2X$ ULN and alkaline phosphatase (ALP) $< 2X$ ULN |
| <ol style="list-style-type: none">1. The subject should <i>interrupt</i> investigational study drug.2. Refer to the “<i>Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials</i>” (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 study drug may be restarted with approval by the Sponsor. Otherwise, the subject should discontinue treatment with investigational study drug. <p>Note: Laboratory assessments prescribed in the <i>Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials</i> may be sent locally in emergent cases and to support subject compliance with the necessary evaluations. Subjects unwilling to undergo the prescribed testing should be discontinued from treatment with investigational study drug.</p> |

| |
|--|
| B) Subject has: <ul style="list-style-type: none">• ALT or AST $\geq 8X$ ULN <u>OR</u>• ALT or AST $\geq 3X$ ULN and signs or symptoms of a drug reaction consistent with liver injury (eg, fever, eosinophilia, right upper quadrant pain, dark urine, fatigue, etc.) |
| <ol style="list-style-type: none">1. The subject should <i>interrupt</i> investigational study drug.2. Perform repeat ALT and AST within 3 days of receipt of the laboratory report.3. Initiate evaluation for potential causes. See Section II below.4. Repeat ALT and AST tests at appropriate intervals, initially approximately 2-times per week, until resolution or return to baseline.5. If an etiology for the elevated liver enzymes is established (eg, active hepatitis with specific etiology demonstrated, cholecystitis, biliary obstruction), investigational study drug may be restarted with approval by the Sponsor. Otherwise, the subject should discontinue treatment with investigational study drug. <p>Note: Local laboratory assessments can be used to support compliance with the repeat testing procedure described above if required. Subjects unwilling to undergo repeat ALT and AST testing at the frequency recommended above should be discontinued from treatment with investigational study drug.</p> |

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C) Subject has:

- **ALT or AST $\geq 3X$ and $< 8X$ ULN**

1. For subjects with:

ALT or AST $\geq 3X$ and $< 5X$ ULN:

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

OR

ALT or AST $\geq 5X$ ULN and $< 8X$ ULN:

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

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

3. Actions based upon *initial* repeat testing:

If **ALT or AST $\geq 3X$ ULN with TBL $\geq 2X$ ULN**, then interrupt investigational study drug 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 $\geq 8X$ ULN or ALT or AST $\geq 3X$ ULN with symptoms** present (eg, fever, eosinophilia, right upper quadrant pain, dark urine, fatigue, etc.), then interrupt investigational study drug and monitor as described in Section B Instructions above.

If **ALT or AST $\geq 3X$ 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 $\geq 5X$ 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 $\geq 5X$ ULN** after 2 weeks, *discontinue investigational study drug*.

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

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

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

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

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

Section II: Guidance for Assessment of Potential Etiology

Questions to Assess Etiology

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

1. Has the subject recently:
 - Had a change in his/her pattern of alcohol use? Investigate historic pattern of alcohol use as well.
 - Administered an illegal drug(s) (including intravenous drugs)?
 - Been exposed to a chemical agent or other environmental toxin?
 - Consumed any unusual foods (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; methyl dopa; 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 7.8.1](#) for details).

The following potential cardiovascular SAEs will not be subject to expedited reporting by the Sponsor, even if reported as related to study drug by the Investigator, unless and until the event is reviewed by the EAC and found not to meet the specified criteria in the EAC charter for that event type:

1. Cardiovascular deaths.

2. Non-fatal myocardial infarction; hospitalization for chest pain or to rule out myocardial infarction, or other hospitalization due to suspected myocardial ischemia where myocardial infarction needs to be ruled out.
3. Non-fatal stroke; TIA, reversible ischemic neurologic deficit (RIND) or other acute ischemic cerebrovascular event where stroke needs to be ruled out.
4. Hospitalization for unstable angina.

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

With respect to the primary endpoint of reduction in HbA1c from Baseline to Week 26 and assuming an SD of 1.0%,¹¹ the sample size of approximately 600 subjects (200 per arm) provides at least 99% power to detect a difference of 0.5% between each ertugliflozin dose and placebo (and 98% power for detecting this difference for both doses vs placebo) using a two-sided 0.05 alpha level test, allowing for a dropout rate of up to 20%. To control the overall Type I error rate at 0.05 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.

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The sample size for this trial also provides adequate precision for the comparisons of ertugliflozin versus placebo with respect to the changes in BMD from Baseline to Week 26. In a recent study of another SGLT2 inhibitor (dapagliflozin) in subjects with inadequately controlled T2DM on metformin, the largest variability for the change from baseline in BMD was at the total hip site, with a standard deviation (SD) of approximately 3.3% after 50 weeks.¹³ Assuming that the SD of the change in BMD increases over time, 3.3% was taken as a conservative estimate of the variability at 26 weeks for precision calculations and also to ensure adequate precision for all BMD sites.

Assuming an SD of 3.3% and allowing for a dropout rate of up to 15% at Week 26, the half-width of the 95% confidence interval for the between-treatment difference is expected to be $\pm 0.7\%$ from the point estimate for the overall study population, and also of approximately $\pm 1.0\%$ for the post-menopausal for ≥ 3 years sub-group which will be analyzed separately (approximately 50% of the overall study population). These CI half-widths would be precise enough to rule out clinically relevant changes in BMD, both for the overall study population and the ≥ 3 years post-menopausal subgroup. This is based on changes in BMD that are approximately 50% of the average changes from baseline to Week 80 observed for thiazolidinediones, which are known to be associated with significant bone loss and an increased risk of fracture.¹⁹

BMD data will not be censored at the point of a subject taking glycemic rescue therapy, so the dropout rate assumed for precision calculation (15%) is lower than that assumed for the HbA1c power calculation (20%). However BMD data will be censored at the point of a subject taking BMD rescue therapy.

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 Phase A of the trial including baseline and post-baseline time points. The post-glycemic rescue therapy data from subjects who require rescue therapy prior to week 26 will be censored from primary and secondary endpoint 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:

- Treatment (categorical),
- Visit (categorical),
- Treatment by visit interaction,
- Menopausal Status randomization stratum.

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.¹⁶ 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.

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 treatment (categorical), randomization stratum (categorical), and baseline value (continuous). 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. Other additional analyses to explore the robustness of results to regions and other factors will also be performed.

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

9.2.2. Analysis of Secondary Endpoints

The proportion of subjects achieving an HbA1c <7% (53 mmol/mol) at Week 26 will be analyzed using a logistic regression model with terms for treatment (categorical), Baseline HbA1c (continuous). Summary measures from the analysis will include the odds ratio, 95% confidence interval for the odds ratio, and p-value for the comparison of treatment groups.

The secondary endpoints of fasting plasma glucose, body weight, 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.

The secondary efficacy endpoints of FPG, proportion of subjects achieving an HbA1c <7%, 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. A step-down hierarchical, sequential testing approach will be used, as follows:

| Order | Endpoint (Change from Baseline to Week 26*) | Arm Comparison |
|---|---|------------------------------------|
| 1 | HbA1c | 15 mg ertugliflozin arm to placebo |
| 2 | HbA1c | 5 mg ertugliflozin arm to placebo |
| 3 | FPG | 15 mg ertugliflozin arm to placebo |
| 4 | FPG | 5 mg ertugliflozin arm to placebo |
| 5 | Body Weight | 15 mg ertugliflozin arm to placebo |
| 6 | Body Weight | 5 mg ertugliflozin arm to placebo |
| 7 | HbA1c <7.0% at Wk 26 | 15 mg ertugliflozin arm to placebo |
| 8 | HbA1c <7.0% at Wk 26 | 5 mg ertugliflozin arm to placebo |
| 9 | Systolic BP | 15 mg ertugliflozin arm to placebo |
| 10 | Systolic BP | 5 mg ertugliflozin arm to placebo |
| 11 | Diastolic BP | 15 mg ertugliflozin arm to placebo |
| 12 | Diastolic BP | 5 mg ertugliflozin arm to placebo |
| *Except for HbA1c <7.0% at Wk 26 endpoint | | |

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 will be tested at a 5% level of significance. Otherwise, testing ceases within this hierarchy.

9.2.3. Analysis of Other Secondary Endpoints

9.2.3.1. Analysis of BMD

The changes in BMD from Baseline to Week 26 at the lumbar spine, femoral neck, total hip, and distal forearm will be key safety endpoints. A BMD analysis set will be defined to include all randomized subjects who have received at least one dose of investigational product and have at least one measurement of BMD at any time during Phase A of the trial including baseline and post-baseline time points. For analyses of changes in BMD, measurements obtained post glycemic rescue therapy will be utilized if available; however BMD measurements will be censored at the point of a subject taking BMD rescue therapy.

Changes from Baseline to Week 26 in BMD will be analyzed by fitting a constrained longitudinal data analysis model with terms for treatment, visit, treatment by-visit interaction and menopausal status randomization stratum. Least-squares means and 95% confidence intervals will be used to estimate the treatment effect (difference between ertugliflozin and placebo) at Week 26.

Analyses of BMD will also be conducted separately for the male and female subgroups and also for subjects who completed ≥ 20 weeks of study treatment. Another sub-group analysis will be conducted separately for women post-menopausal for ≥ 3 years after LMP

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(approximately 50% of the overall study population). Descriptive statistics will also be provided for each of the four randomization strata.

Changes from baseline in other continuous endpoints (including bone biomarkers) will be summarized descriptively (including 95% confidence intervals for BMD endpoints) by treatment group (for all treatment arms in each phase) and time point. Categorical endpoints will be summarized using frequency tables for each treatment group and time point.

Bone biomarker data and PTH data will be censored from the analysis if the samples were collected >7 days from the last dose of investigational product. Data for these markers will also be censored for subjects who initiate rescue medication with any bone-active medication.

9.2.4. 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 safety analysis population will consist of all treated subjects, ie, all subjects who received at least one dose of investigational product.

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 consists of pre-specified adverse events of interest, and will include AEs or collections of AEs related to urinary tract infection, genital mycotic infection, 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

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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 are provided for screening purposes only. 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. Planned Analyses

The results of Phase A will be analyzed, and a clinical study report for Phase A will be written while Phase B is on-going. The results of Phase A will not be used to make any changes to the design or conduct of Phase B. An unblinding plan will be developed and put into place in order to limit the extent of sponsor unblinding that takes place during the reporting of Phase A and to ensure that sponsor staff who interact with clinical sites do not have access to treatment assignments during Phase B.

No formal interim analyses are planned (other than in support of the independent DMC regular review of safety), but may be conducted if necessary in support of Regulatory filings or requests.

9.5. 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 and a separate E-DMC Charter will describe the precise mandates of the E-DMC. The recommendations made by the E-DMC to alter the conduct of the trial will be forwarded to the Sponsor for final decision. The 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.

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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),

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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.

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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.

12.3.1. Informed Consent for Future Biomedical Research

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

12.4. 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

13.1. End of Trial in a Member State

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

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13.2. End of Trial in all Other Participating Countries

End of Trial in all other participating countries 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 ClinicalTrials.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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Appendix 1. Collection and Management of Specimens for Future Biomedical Research

1. Scope of Future Biomedical Research

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

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

2. Definitions

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

3. Summary of Procedures for Future Biomedical Research

- a. Subjects for Enrollment

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

- b. Informed Consent

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

² International Conference on Harmonization: Definitions For Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories - E15; <http://www.ich.org/LOB/media/MEDIA3383.pdf>.

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

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

Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main study.

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

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5. Biorepository Specimen Usage

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

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

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10. Gender, Ethnicity, and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

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

12. Self-Reported Ethnicity

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

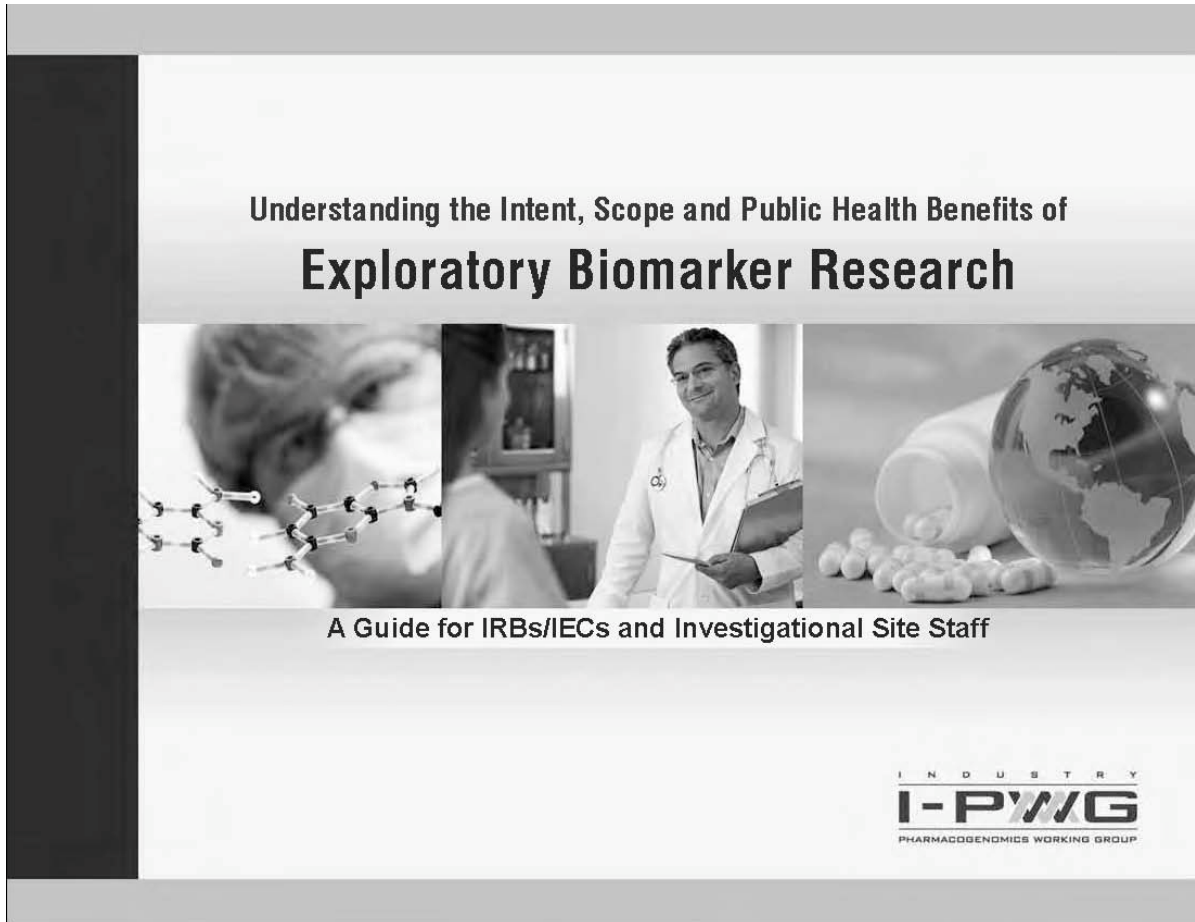
13. Questions

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

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Appendix 2. Biomarker Brochure



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

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

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

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

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure² and ICH Guidance E15³ for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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

3. Importance of Biomarkers to Regulatory Authorities

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

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

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

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

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

5. Biomarkers are Already a Reality in Health Care

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

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2neu* overexpression analysis required for prescribing trastuzumab (Herceptin[®]) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec[®]) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix[®]) or cetuximab (Erbix[®]) to metastatic colorectal cancer patients.

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

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

rogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

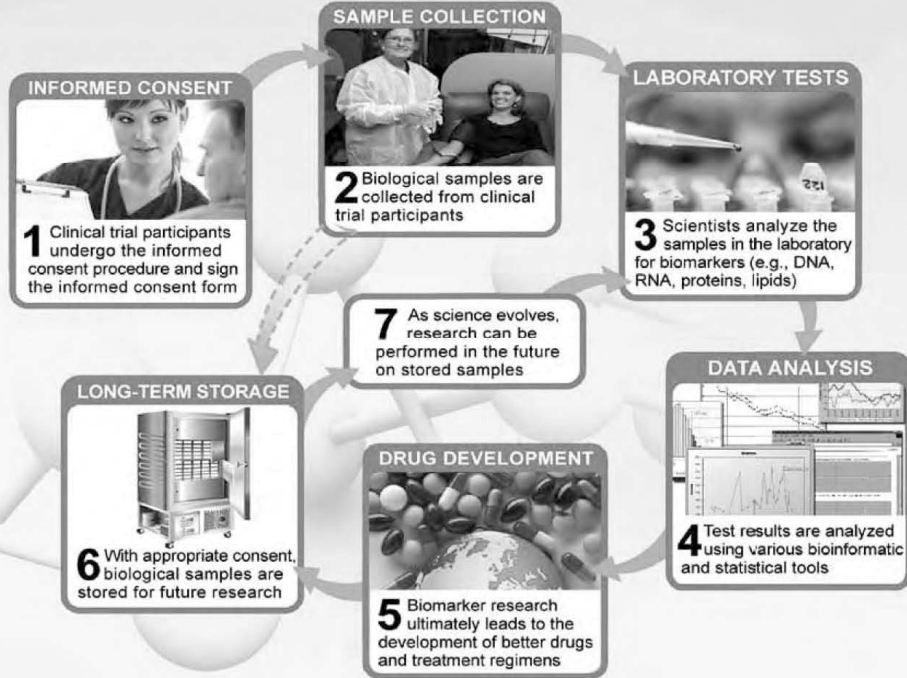
Important elements of informed consent for **future use** of samples include, but are not limited to:³³

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

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.³ In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.³³

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

Biomarker Research in Clinical Trials



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8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

- i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)
- ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable
- iii) whether genetic counseling is recommended (for genetic results)
- iv) the ability to accurately link the result to the individual from whom the sample was collected
- v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

The humanitarian benefit of human research is recognized by the Nuremberg Code.^{26,33} Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.^{26,32}

Risks

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

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways:

- i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12. Where to Get More Information?

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

13. What is I-PWG?

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

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

14. Contributing authors

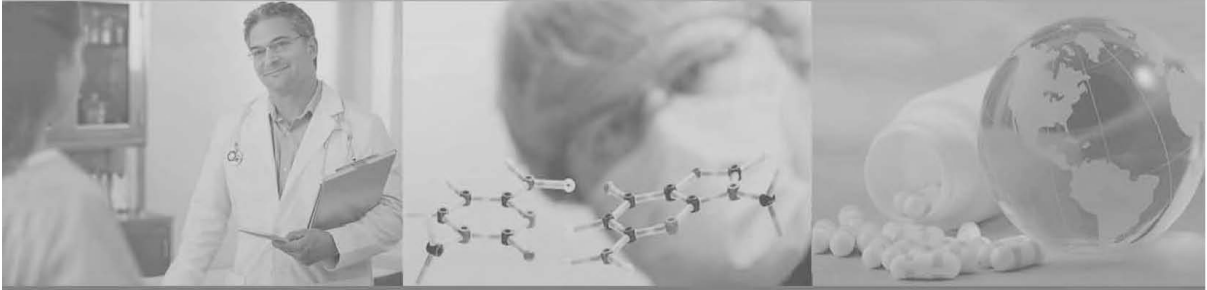
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